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Abstract Reference List

Reviews of Pertinent Literature in Shock

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13 February 1978

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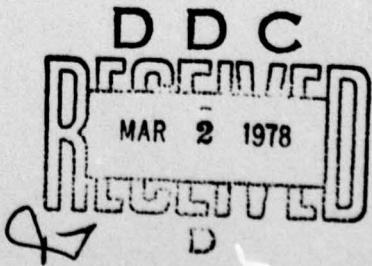


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1. Pulmonary microembolism in early experimental septic shock: A morphological study in dogs. H. E. Myrvold and C. Svalander. J. Surg. Res. 23: 65-74, 1977.

In 1958 Kuida and associates described the characteristic pulmonary hemodynamic pressor response in dogs after injection of Escherichia coli endotoxin. The changes in pulmonary vascular resistance after endotoxin injection, and the subsequent tissue damage, have been ascribed to mechanical blocking at the capillary level by platelet aggregates, release of humoral factors, leukocyte sequestration, disseminated intravascular coagulation, or combinations of these factors.

The ultrastructure of the dog lung was studied during the early phase after iv injection of disintegrated Pseudomonas bacteria. The findings were related to the initial pulmonary pressure response and the initial reaction of platelets, polymorphonuclear leukocytes, and fibrinogen. Platelet aggregates, polymorphonuclear leukocyte disintegration, and ultrastructural endothelial damage were found in the pulmonary capillaries within 2-5 min after injection of bacterial toxin, but there were no signs of fibrin precipitates during the 2 hr of the experiment. Essentially the same morphological changes were found in dogs who were defibrinogenated or made thrombocytopenic. Platelet aggregates, disintegrated leukocytes, and endothelial changes were found in defibrinogenated dogs, and disintegrated leukocytes and endothelial changes were found in the thrombocytopenic dogs.

Since thrombocytopenia attenuates the pulmonary hemodynamic response after bacterial toxin, the results indicate that platelet aggregates trapped in the pulmonary microcirculation are of importance for the hemodynamic response, but not for the endothelial damage found. The accumulation of platelets in the lungs is rapid and reversible. Endothelial damage occurs within minutes and seems to be related to the sequestration and disintegration of polymorphonuclear leukocytes, or to a direct effect of the bacterial toxin. Defibrinogenation, which does not influence the hemodynamic response, did not prevent endothelial damage.

2. Current understanding of mechanisms and treatment of circulatory shock caused by bacterial infections. M. Weil. Ann. Clin. Res. 9: 181-191, 1977.

Shock is a descriptive term used by clinicians to denote a syndrome characterized by protracted prostration, with pallor, coldness and moistness of the skin, collapse of superficial veins, alterations of mental status, and suppression of the formation of urine. The physiological defect which underlies the shock state is acute circulatory failure with reduction of effective blood flow to the skin and especially the extremities, to muscle, to the brain, to the kidneys, and to other vital organs. Critical reductions in blood flow, which is more precisely termed perfusion failure, explain the clinical signs of shock including hypotension which represents a lowering of side wall pressure in the arterial (resistance) circuit.

Bacteremia caused by gram-negative enteric organisms accounts for the majority of instances of shock complicating bacterial infection. Control of the infection and maintenance of normal blood volume constitute the primary considerations in immediate treatment. The use of three or four

doses of corticosteroid agent over a period of 24 hours is regarded by this group as advantageous for routine treatment. Conservative and selective use of dopamine and phentolamine are justified for management of patients who do not respond to the administration of bactericidal drugs and volume repletion. Levarterenol and metaraminol are rarely indicated. With more effective management of the hemodynamic defects, patients are now more likely to survive the shock state only to develop a fatal form of pulmonary failure which as yet is poorly understood. Close attention to respiratory management is therefore advised.

3. Intravascular coagulation and fibrinolysis. R. L. Palmer. Postgrad. Med. 62: 181-187, 1977.

Intravascular coagulation occurs as a sequela of many diverse conditions and may vary greatly in clinical and laboratory manifestations. The essence of the problem is that plasma is converted to serum in the circulation. As a result, both hemorrhagic and thrombotic events may occur. Platelet count and fibrinogen determination are the most important diagnostic tests. If values are abnormal, tests for fibrin (fibrinogen) degradation products are indicated.

The first step in management is to identify and attempt to eliminate the underlying cause. Heparin therapy should be considered, particularly when clotting and severe fibrinolysis are both present. Replacement of clotting factors may be considered, but its value is a matter of debate.

4. Granulocyte transfusions in recovery of neutropenic rats from induced *E. coli* toxicemia. V. Popovic, R. Schaffer and P. Popovic. Exp. Hemat. 5: 166-170, 1977.

Rats made transiently neutropenic by intra-arterial administration of vinblastine (3 mg/kg) and infected with *E. coli* ( $6.02 \pm 0.45 \times 10^8$ , per animal) have a mortality rate of 90% within 48 hr post infection. Multiple transfusions of large numbers of granulocytes (harvested from Deca-Durabolin treated donor rats) protected the neutropenic animals from sepsis. Out of a group of 11 rats, 10 recovered completely after repeated granulocyte transfusions.

5. Variations in adrenocortical responsiveness during severe bacterial infections. Unrecognized adrenocortical insufficiency in severe bacterial infections. W. J. Sibbald, A. Short, M. P. Cohen, and R. F. Wilson. Ann. Surg. 186: 29-33, 1977.

Plasma cortisol levels and their response to .25 mg synthetic ACTH (Cortrosyn) were studied in 26 septic patients. Four (15.4%) of these patients appeared to have greatly increased adrenocortical activity with plasma cortisol levels averaging  $65.4 \pm 14.8 \mu\text{g/dl}$  (normal=8-18  $\mu\text{g/dl}$ ). All four of these patients were agonal and died within 5 days. Seventeen (65.4%) of these 26 patients appeared to have an appropriate adrenocortical response to severe infection in that their plasma cortisol levels increased (averaging  $19.2 \pm 6.0 \mu\text{g/dl}$ ) following synthetic ACTH. The remaining 5 patients, who constituted 19.2% of the 26 patients studied, appeared to have some impairment of adrenocortical function. In spite of severe bacterial infections and no history

to support Addison's disease, their plasma cortisol levels (averaging  $13.8 \pm 3.3 \mu\text{g/dl}$ ) were not increased above normal and their response to Cortrosyn was much less than would be expected; the increase in plasma cortisol levels in these patients following the synthetic ACTH averaged  $1.1 \pm 3.6 \mu\text{g/dl}$ . It is reemphasized that patients with severe sepsis who are not responding adequately to standard therapy should be suspected of having adrenocortical insufficiency and treated accordingly.

6. Cardiorespiratory effects of Pseudomonas and E. coli endotoxins in the awake dog. T. H. Miller, L. L. Priano, J. H. Jorgensen, and D. L. Traber. Am. J. Physiol. 232: H682-689, 1977.

A comparison of the cardiovascular and respiratory effects of Pseudomonas aeruginosa and Escherichia coli endotoxins was investigated in the unanesthetized dog. Animals were anesthetized with halothane for placement of cardiovascular catheters and then allowed to awaken prior to collection of control data and experimentation. One group of 12 animals was given E. coli endotoxin (5 mg/kg), another group of 13 received Pseudomonas endotoxin (8 mg/kg). Variables were collected for 6 hr after endotoxin injection. A third group of 13 animals serving as sham animals received no endotoxin. When major cardiovascular variables, such as arterial blood pressure, cardiac output, right atrial pressure, and left ventricular pressure and dP/dt were monitored, it was seen that the basic patterns of response to endotoxins were quite similar, with differences between groups being primarily quantitative. Analysis of respiratory data showed that animals receiving Pseudomonas developed an earlier respiratory response. Nevertheless, blood gas data were similar in the two groups.

7. Clinical pharmacology of systemic corticosteroids. J. C. Melby. Ann. Rev. Pharmacol. Toxicol. 17: 511-527, 1977.

It is more than a quarter of century since Hench showed the prompt and dramatic reversal of the inflammatory manifestations of rheumatoid arthritis after the administration of cortisone. In 1971, Christy estimated that more than 5 million patients were treated with corticosteroids yearly. From this enormous experience and from a massive literature, concepts have evolved regarding the safe and effective use of these agents. An obvious generalization is that corticosteroid therapy is most often temporary and adjunctive. The corticosteroids allow the host to recover in self-limited conditions and to suppress some manifestations of chronic diseases that reappear when corticosteroids are withdrawn. It is predominantly in patients with chronic diseases that the deleterious effects of the corticosteroids are most prominent.

In this discussion, the clinical pharmacology of systemic corticosteroid administration and concepts of systemic corticosteroid therapy are examined. The special problem of suppression of the hypothalamic-pituitary-adrenal system is emphasized.

8. Catecholamines in shock. A. Alho, A. Jäättelä, M. Lahdensuu, P. Rokkanen, V. Avikainen, E. Karaharju, T. Tervo, and P. Lepistö. Ann. Clin. Res. 9: 157-163, 1977.

The role of endogenous catecholamines in various clinical shock and stress states is reviewed; the effects, especially on the peripheral circulation, of catecholamine secretion are the same independent of the cause. Risks

of using sympathomimetic agents in the treatment of shock are evaluated. A prolonged noradrenaline activity is to be expected in surgical stress states, e.g. multiple injuries, fat embolism syndrome, burns and infections; therapeutic approaches to minimize the sympathoadrenal activity are outlined.

9. Pathophysiology and fluid replacement in hypovolemic shock. G. T. Shires. Ann. Clin. Res. 9: 144-150, 1977.

Fluid management in the severely injured patient basically involves the prompt recognition and treatment of hemorrhagic shock to prevent the complications and reduce the mortality resulting from prolonged inadequate tissue perfusion. In addition, losses of functional extracellular fluid associated with hemorrhagic shock or sequestered into the areas of injury (third space losses) may aggravate the shock state and may be difficult to recognize and quantitate. An attempt is made here to present a clinical working classification of shock, review several cogent research studies, and, finally, outline the therapeutic concepts of management in patients with hemorrhagic shock and injury.

10. Microembolism in experimental septic shock. H. E. Myrvold and A. Brandberg. Eur. Surg. Res. 9: 34-47, 1977.

Platelets were labelled with  $^{51}\text{Cr}$ , fibrinogen with  $^{123}\text{I}$  and erythrocytes with  $^{59}\text{Fe}$ . Disintegrated Pseudomonas bacteria were injected intravenously and radioactive measurements were made on whole blood, tissue biopsies and clottable fibrinogen. After the injection there was an immediate but transient increase of  $^{51}\text{Cr}$  activity in the lung concomitant with a decrease in platelet count and  $^{51}\text{Cr}$  activity of blood. In the liver there was a less pronounced increase of  $^{51}\text{Cr}$  activity. The fibrinogen concentration decreased slightly, paralleled by the  $^{123}\text{I}$  activity of whole blood and of clottable fibrinogen, whereas the  $^{123}\text{I}$  activity in the lung and liver remained fairly constant. There were no changes of  $^{51}\text{Cr}$  activity or  $^{123}\text{I}$  activity in biopsies from muscle, pancreas, small intestine, kidney or spleen. During the experiment (3 hr) there were no signs of significant disseminated intravascular coagulation other than platelet aggregation. A consumption of fibrinogen related to the formation of fibrin plugs could not be detected. After injection of disintegrated Pseudomonas bacteria reversible platelet aggregates were formed and temporarily trapped in the pulmonary microcirculation. This microembolism might induce tissue damage and could be of importance for the development of septic pulmonary complications.

11. Mechanisms for oliguria in acute renal failure. A. S. Hermreck, F. M. Ruiz-Ocana, K. S. Proberts, R. L. Meisel, and D. G. Crawford. Surgery 82: 141-148, 1977.

Warm ischemic (90 min) acute renal failure (ARF) was evaluated in the dog and found to cause polyuric ARF in the injured kidney if the opposite normal kidney was removed. In contrast, if the normal kidney were left intact, oliguric ARF was noted in the injured kidney. To further evaluate the mechanisms for oliguria and polyuria, chronic reinfusion of urine from a normal kidney into the inferior vena cava (ureterocaval anastomosis) resulted in polyuria in the opposite warm ischemic injured kidney; whereas chronic reinfusion of urine into the portal vein (ureteroportal anastomosis) resulted in profound oliguria in the opposite injured kidney. In separate

additional experiments, urine acutely infused into the inferior vena cava at a rate of 0.38 ml/min caused a significantly greater diuretic and renal hemodynamic response than seen with urine infused into the portal vein. Acute infusions of urea solution (0.38 ml/min) with the same osmolality of urine were completely devoid of diuretic and renal hemodynamic effects. These studies reveal that urine contains a powerful hemodynamic and diuretic factor which appears to convert oliguric to polyuric ARF following warm ischemic renal injury in the dog. This factor is not urea and can be destroyed by the liver.

12. A rapid method for determining the percentage of antibacterial phagocytes in a sample population of leukocytes. W. A. Janssen and H. G. Dangerfield. J. Reticuloendo. Soc. 21: 299-306, 1977.

A relatively rapid, simple, direct microscopic assay of the antibacterial capability of phagocyte populations has been developed. Normal mice or mice treated with 7.6% sodium caseinate to stimulate production of peritoneal exudate cells were inoculated ip with actively growing Vibrio parahemolyticus at estimated ratios of 1:5 vibrios per phagocyte. Thirty min later phagocytes were harvested by washing the peritoneal cavity with 2 ml of a harvest medium that arrested phagocytosis but permitted viable intra- and extracellular vibrios to form microcolonies after incubation for 2 hr at 37°C on microscope slides. The antibacterial potential of the phagocyte population was determined by comparing the percentage of phagocytes with ingested vibrios before culture with the percentage of phagocytes whose intracellular V. parahemolyticus failed to replicate after incubation. Essentially all phagocytic cells in peritoneal washings from normal mice were found to be macrophages, less than 50% of which had antibacterial activity against V. parahemolyticus. Antibacterial phagocyte populations were greatly increased following exudate induction; within 1 hr the macrophage population doubled and the percentage of antibacterial macrophages was increasing; within 4 hr the exudates contained both neutrophils and macrophages and essentially all phagocytizing cells had effective antibacterial capability. This technique, employing an in vivo milieu for phagocyte-bacterial interactions, provides optimum conditions for assays of phagocyte antibacterial capability and its modification by treatment of the donor.

13. Role of the pancreas in stability of mitochondrial function in hemorrhagic shock. M. Sato, M. Yamamoto, K. Ozawa, and I. Honjo. J. Surg. Res. 23: 19-24, 1977.

The pancreatectomized rats showed the more rapid depletion of energy stores during hemorrhagic shock than the non-pancreatectomized animals. In pancreatectomized rats the oxidative and phosphorylative activities of the mitochondria decreased markedly to about 40% of the preshocked levels at 1 hr after hemorrhagic shock, though those in control rats remained almost unchanged. The decreases in mitochondrial oxidative and phosphorylative activities and hepatic energy charge levels in pancreatectomized rats were not restored by the reinfusion of the shed blood after 1-hr hemorrhagic shock. Thus, it is suggested that the pancreas plays an important role in hepatic energy metabolism during hemorrhagic shock, possibly due to maintaining the integrity of mitochondrial membrane.

14. Glucose-dependent hepatic membrane transport in nonbacteremic and bacteremic thermally injured patients. W. C. McDougal, D. W. Wilmore, and B. A. Pruitt, Jr. J. Surg. Res. 22: 697-708, 1977.

Hepatic clearance of indocyanine green was measured in 106 studies in 25 thermally injured patients with an average total body surface burn of 59% and a mean age of 35 years. Seventeen patients subsequently developed positive blood cultures and were restudied. Fourteen serial measurements of dye concentration taken over a 70-min period were computer fitted to describe each disappearance curve, and the two rate constants,  $k_1$  and  $k_2$ , were determined (all  $r^2 > 0.94$ ).

ICG plasma disappearance was unimpaired in nonbacteremic patients when glucose or glucose plus amino acids were part of the parenteral regimen ( $-k_1 = 0.241 \pm 0.023$  and  $0.255 \pm 0.009 \text{ min}^{-1}$ ) but significantly decreased when near isocaloric amounts of glucose-free amino acid solutions were administered ( $-k_1 = 0.150 \pm 0.016 \text{ min}^{-1}$ ,  $p < 0.001$ ). Bacteremic patients had markedly impaired ICG hepatic clearance irrespective of the hypocaloric dietary regimen. Both exclusion of glucose from the nutrient infusates in nonbacteremic patients and bacteremia result in a marked reduction in the maximal velocity of the ICG dye transport reaction.

Septic patients infused with glucose and insulin improved their clearance of the dye (from  $k_1 = 0.169 \pm 0.029$  to  $0.183 \pm 0.028 \text{ min}^{-1}$ ,  $p < 0.01$ ). These alterations could not be related to changes in circulation or perfusion. Urea production varied inversely and endogenous insulin levels directly with the  $k_1$ , suggesting that membrane transport is related to the ornithine cycle and/or is influenced by insulin.

Optimal metabolic integrity of the hepatocyte is substrate specific and dependent upon the provision of exogenous energy. Hepatic transport function is limited in bacteremic patients as well as burn patients who are deprived of glucose. Restoration of hepatic transport processes may be achieved by providing sufficient energy in the form of glucose.

15. Ejection pressure and the diastolic left ventricular pressure-volume relation. J. S. Janicki and K. T. Weber. Am. J. Physiol. 232: H545-552, 1977.

The influence of ejection pressure (EP) on the left ventricular end-diastolic pressure-volume (P-V) relation was examined in 24 paced, isolated canine hearts. A pressure servo system was used to control DP and monitor ventricular volume. For any given contractile state EP was varied: a) by 10- to 20-mmHg increments and the steady-state P-V response observed at each EP level (method A); or b) by instantaneously attaining the isovolumic condition ( $P_0$ ) from a given EDV and examining the immediate P-V response (method B). With either method it was possible to alter the P-V relation; the maximum variation occurred when, for a given EDV or EDP, EP was raised from a value  $< 50\%$  of its corresponding peak osovolumic pressure to  $P_0$ . For the EDP range 2-25 mmHg, the direction and total magnitude of change were: 1) an increase in EDV 1.3-9 ml was required to maintain EDP constant; and 2) for a constant EDV, EDP decreased an average  $16.5\% \pm 1.2 \text{ SE}$  (6-23.9%;  $p < .02$ ). The EDP decline observed with method B was immediate and reversible within several beats upon returning to the ejecting mode. Thus, under the conditions of this experiment the diastolic pressure-volume relation is a physiological variable dependent on ejection pressure.

16. Interaction of aortic pressure and left ventricular end-diastolic pressure in the dog. J. R. Foster, E. R. Powers, and W. J. Powell, Jr. Am. J. Physiol. 232: H697-H704, 1977.

Fiber length (preload) is an important determinant of left ventricular performance. Mean aortic blood pressure also influences ventricular performance. The present study was undertaken to examine the influence of mean aortic pressure on the fiber length-ventricular performance relationship. Fifteen anesthetized, adrenergically blocked dogs were studied on right-heart bypass at constant heart rate and coronary blood flow. An increase in mean aortic pressure permitted a greater improvement in performance as evaluated by stroke work for a given increase in left ventricular end-diastolic pressure. A given increase in mean aortic pressure at a constant stroke volume produced a greater rise in stroke work over intermediate ranges of left ventricular end-diastolic pressure than occurred with higher or lower left ventricular end-diastolic pressure. Thus, the degree of afterload-induced performance improvement depended on the magnitude of the preload. External circumference-left ventricular end-diastolic pressure data suggested a possible relationship between isovolumic systolic circumferential expansion and the improvement of ventricular performance at higher mean aortic pressures.

17. Flow-induced trauma to blood cells. S. P. Sutera. Circ. Res. 41: 2-8, 1977.

A considerable amount of research has been done on flow-induced trauma to blood cells. Much is now known concerning the nature of the trauma and the minimum levels of (sustained) shear stress required to lyse cells in vitro. As these levels are generally higher than those which blood cells encounter either in normal physiological circumstances or in a well functioning extracorporeal circuit, it seems logical to conclude that cell-surface interactions, probably influenced by shearing flow, are the primary cause of blood damage when it occurs in such circumstances. If correct, this conclusion means that resolution of the blood trauma problem is going to be very difficult because, although the engineer can design a system so as to keep the maximum shear stress within a prescribed bound, he cannot eliminate manmade containing surfaces. This fact, as alluded to many times in the discussion of this article, has even posed a persistent obstacle in the way of clear interpretation of the experimental data on shear-induced trauma.

The evidence gathered to date indicate clearly that leukocytes are susceptible to flow-induced trauma. Although their precise fragility under shearing stress remains to be determined, it appears that potentially dangerous functional impairment can occur. Sequestration of damaged, perhaps less deformable leukocytes in the lung, leading to elevated pulmonary resistance and right ventricular hypertension, and decreased protection from infection are two possible consequences. Certainly the subject of leukocyte trauma deserves more research and there is every reason to expect that more experimental data on these complicated and interesting cells are forthcoming.

18. Vasopressin and canine hepatic arterial blood flow. J. C. Kerr, D. G. Reynolds, and K. G. Swan. J. Surg. Res. 23: 166-171, 1977.

The effects of intra-arterial vasopressin upon canine hepatic arterial blood flow were investigated to determine the possible ischemic hazard to the liver by this agent when utilized for the clinical control of gastrointestinal hemorrhage. When injected in concentrations ranging logarithmically from  $5 \times 10^{-5}$  to  $5 \times 10^{-2}$  units  $\text{kg}^{-1}$ , vasopressin produced a dose-dependent diminution in flow. At the highest concentration, vasopressin reduced flow by  $199 \pm 43 \text{ ml min}^{-1}$  and increased aortic pressure by  $13 \pm 2 \text{ mmHg}$ . This same concentration of vasopressin reduced portal venous pressure by  $1.8 \pm 0.2 \text{ mmHg}$ . These observations in dogs indicate that vasopressin is a potent constrictor of the hepatic artery. They also suggest that the clinical use of vasopressin to control upper gastrointestinal bleeding in man is unlikely to pose any threat of significant ischemia to the liver, as has been suggested in the past.

19. Insulin, glucagon, portal systemic shunting, and hepatic failure in the dog. P. B. Soeters, G. Weir, A. M. Ebeid, and J. F. Fischer. J. Surg. Res. 23: 183-188, 1977.

Previous work from this as well as other laboratories has provided some evidence that hepatic encephalopathy may be related to deranged amino acid patterns. Normalization of these patterns by infusion or dialysis techniques may result in awakening in hepatic coma. The purpose of this study, that of insulin and glucagon measurements in hepatic encephalopathy, was to provide some appreciation of the possible roles of insulin and glucagon in the pathogenesis of hepatic failure. We have attempted to use a well-controlled animal model in attempting to define the respective role of shunting and decreased hepatic function to the hyperinsulinemia and hyperglucagonemia which accompany hepatic decompensation.

20. Bacterial toxins as virulence factors: Shiga bacillus dysentery viewed as a toxinosis. G. T. Keusch. Mt. Sinai J. Med. 43: 33-41, 1976.

Toxins are molecules produced by living cells with biological activity (either destructive or stimulatory) which results in disease symptoms in the host. A second major criterion defining toxins which is generally accepted is that these molecules are proteins, whether simple or complex. Thus bacterial cell wall lipopolysaccharide, also called endotoxin, is not a true toxin at all. Lipopolysaccharide, while of organic origin and biologically active, may be detoxified by non-immune mechanisms. A further distinction between the protein toxins and lipopolysaccharide is that the former have specific biochemical actions or enzymatic activity whereas the latter acts "non-specifically".

Reference to lipopolysaccharide as endotoxin to distinguish this material from protein exotoxins, such as botulinus exotoxin, uses the bacterial cell as a geographic frame of reference. Toxic materials associated with the bacterial cells are called endotoxins, whereas exotoxins are released into the extra-cellular medium. However this differentiation is highly artificial, and depends upon conditions of bacterial growth, time of sampling and the particular toxin in question.

It is not possible to remove by fiat, however compelling the logic, terms so firmly fixed in the medical literature such as endotoxin and exotoxin. As a distinction of chemical nature rather than anatomic localization there is a potential use in retaining the terms. However, the recent explosive advance in knowledge of diarrhea-producing protein enterotoxins and the frequent confusion between entero- and endotoxin, indicates that the terms endo- and exotoxins have indeed outlived their historical value--they now contribute more to confusion than understanding. A conscious effort to speak only of lipopolysaccharide and of protein toxins and to exorcise the endo- and exo- classification is not only indicated, but may be the only way to accomplish this change.

21. Glucose utilization and role of blood in endotoxin shock. L. B. Hinshaw, L. T. Archer, B. K. Beller, G. L. White, T. M. Schroeder, and D. D. Holmes. Am. J. Physiol. 233: E71-E79, 1977.

This study was conducted to explore influences modifying glucose uptake in canine blood administered LD<sub>100</sub> *E. coli* endotoxin. Particular emphasis was given to assay the role of the white blood cell (WBC) in glucose utilization. Significant increases in glucose uptake and lactic acid production, attributed to increased activity of the WBC, were observed 1-3 hr after endotoxin was added to blood in vitro. Although a net increase in glucose utilization was noted, endotoxin simultaneously exerted adverse effects by depressing glucose uptake below predicted values ( $Q_{10} = 2.12$  with LD<sub>100</sub> endotoxin vs. 2.78 in saline controls) and increasing WBC mortality rate. Blood from dogs pretreated with sublethal doses of endotoxin in vivo utilized glucose at an accelerated rate when subjected to endotoxin in vitro. Excess glucose was consumed because of elevated numbers of white blood cells although additional glucose requirements after endotoxin were independent of temperature between the ranges of 34-41°C. All animals pretreated with daily sublethal injections of endotoxin for 3 days survived superlethal doses of endotoxin.

22. Unilateral Shwartzman reaction: Cortical necrosis in one kidney following in vivo perfusion with endotoxin. L. Raji, W. F. Keane, and A. F. Michael. Kidney International 12: 91-95, 1977.

Unilateral renal cortical necrosis was selectively induced by in situ perfusion of the rabbit kidney with a perfusate containing 50 µg of endotoxin followed by the i.v. administration of 250 µg of endotoxin 24 hr later. The results strongly support the idea that the initial event in the genesis of renal cortical necrosis during the Shwartzman reaction is a specific local effect of endotoxin on the vascular endothelium.

23. New uses for acetylsalicylic acid and other prostaglandin antagonists. E. M. Cooperman. Canad. Med. Assoc. J. 117: 309-312, 1977.

Review article. No summary available.

24. Catabolic hormones and substrate patterns in septic patients. J. B. Marchuk, R. J. Finley, A. C. Groves, L. I. Wolfe, R. L. Holliday, and J. H. Duff. J. Surg. Res. 23: 177-182, 1977.

Septic patients exhibit rapid muscle wasting and, despite seemingly excellent tissue perfusion, often exhibit stupor, confusion, and individual organ failure. The latter findings suggest profound alterations in metabolism and cellular function which may be more important than abnormalities of blood flow

and pressure in causing the demise of the septic patient.

Hormone and substrate levels were measured in 22 septic and 12 nonseptic post-operative subjects. Plasma glucagon and total plasma catecholamines were increased in the septic subjects suggesting a possible role of these hormones in the severe catabolism of sepsis. There was no difference in the insulin: glucagon (I:G) molar ratios in the two groups, although both groups have a lower ratio than patients who are anabolic while receiving parenteral nutrition. Lack of correlation between I:G ratio and severity of illness in this study would indicate that factors other than insulin and glucagon are operational in the catabolism of sepsis. Catecholamines may have a significant catabolic effect in septic patients. Increased levels of phenylalanine and low serum albumin point to the possibility of impaired liver function in serious septic illness.

25. Cardiac depression in bacteremia. J. Postel and P. Schloerb. Ann. Surg. 186: 74-82, 1977.

Hemodynamic and respiratory effects of a 5-hr iv infusion of *Ps. aeruginosa* at a dose of  $10^8$  organisms per ml per minute were studied in 6 dogs. Four dogs served as controls. Gram-negative bacteremia with  $70,000+1,800$  organisms/ml blood caused a 50% reduction of cardiac output at 3 hrs. Peripheral vascular resistance increased significantly, but mean heart rate fell below control levels. Decline in mean systemic blood pressure from  $150+5$  mmHg to  $88+6$  mmHg was accompanied by a significant increase in pulmonary arterial wedge pressure with normal right atrial and pulmonary arterial pressures. Pulmonary vascular resistance also remained unchanged. With progression of the low output state and development of hypothermia, arterio-venous oxygen difference (A-V  $DO_2$ ) fell significantly. Despite a decline in functional residual capacity, venoarterial admixture diminished in the face of reduced pulmonary capillary perfusion, normal arterial  $PO_2$  values, decline in body temperature and finally very narrow A-V  $DO_2$ . Histologically, ventricular myocardium revealed severe interstitial edema. It is concluded that myocardial dysfunction may occur early during gram-negative bacteremia, and formation of myocardial edema appears to be a significant contributing factor in myocardial failure.

26. Leukocyte transfusions for the prophylaxis and treatment of infections associated with granulocytopenia. J. E. Curtis, R. Hasselback, and D. E. Bergasel. Canad. Med. Assoc. J. 117: 341-345, 1977.

The role of leukocyte transfusions in the prevention and treatment of infections in adults with granulocytopenia was investigated. Leukocytes were obtained from healthy volunteers by continuous-flow centrifugation. Histo-compatibility antigen (HLA)-matched leukocytes were used to assess the prophylactic value of leukocyte transfusions. Seven patients with acute myelogenous leukemia received HLA-matched leukocytes during the period of maximal granulocytopenia associated with initial remission induction therapy, 20 concurrently treated patients who did not receive leukocyte transfusions were the control group. The patients receiving HLA-matched leukocytes had significantly fewer ( $p=0.043$ ) infectious episodes (not bacteriologically proven) during the study period, and remission occurred in 5 of the 7, compared with 10 of the 20 controls.

27. Sepsis in the baboon: Factors affecting resuscitation and pulmonary edema in animals resuscitated with Ringer's lactate versus Plasmanate. J. W. Holcroft, D. D. Trunkey, and M. A. Carpenter. J. Trauma 17: 600-610, 1977.

Patients dying of sepsis or from post-traumatic pulmonary insufficiency frequently have wet, heavy lungs. They also frequently have low serum albumin concentrations. This association of hypoalbuminemia and pulmonary edema has led to suggestions, based on clinical studies, that albumin administration during sepsis might prevent the formation of pulmonary edema by normalizing serum oncotic pressures. The present experiment was designed to study the clinical response of baboons resuscitated from deep septic shock with a pure crystalloid versus pure colloid solution and to measure the amount of pulmonary edema in these baboons *in vivo* by a nonisotopic indicator dilution technique and immediately post-mortem by a gravimetric technique.

Septic shock and the formation of pulmonary edema were studied in 19 baboons. Four animals served as controls. Four were subjected to deep septic shock by infusion of live *E. coli* and then deliberately killed while in deep shock. Four were subjected to septic shock, resuscitated with Ringer's lactate (RL), and then killed 1 1/2 hours after resuscitation was started. Seven were subjected to shock and resuscitation attempted with Plasmanate (PL). Resuscitation with RL was successful for 1 1/2 hours in three of the 7 PL-animals. There was an increased tendency for albumin to extravasate into the interstitium of the lungs after resuscitation. The amount of pulmonary edema, measured by both the thermo-dye technique and by analysis of post-mortem lung composition, was the same in animals resuscitated with RL and PL. Administration of pure colloid offers no protection to the lungs in resuscitating patients from septic shock.

28. The role of assisted circulation in the management of endotoxic shock. J. M. Dunn, M. M. Kirsh, J. Harness, R. Lee, J. Straker, and H. Sloan. Ann. Thor. Surg. 17: 574-583, 1974.

Despite recent advances in treatment, the mortality from endotoxic shock remains high. Death in these patients is frequently associated with progressive myocardial failure. A lethal dose (LD100) of *Escherichia coli* endotoxin (1 mg/kg body weight) was administered intravenously to 12 dogs. The dogs were then divided into two experimental groups of 6 each. The treatment of the dogs in Group I consisted of positive-pressure ventilation and maintenance of circulating blood volume and acid-base balance. The dogs in Group II were treated identically, except that 1 1/2 hours after the induction of endotoxic shock the dogs underwent a period of assisted circulation.

Survival was significantly prolonged in Group II dogs (Group I, 10.6 hrs; Group II, 24.5 hours [ $p<0.01$ ]). In addition, Group II dogs maintained a significantly higher cardiac output ( $p<0.02$ ) and pH ( $p<0.05$ ). They also maintained a greater blood pressure ( $p<0.01$ ) and experienced less metabolic acidosis ( $p<0.8$ ), although these changes were not statistically significant. This study demonstrates the value of prolonged assisted circulation in the treatment of endotoxic shock.

29. Humoral factor activity and carbon clearance rate during the early stages of hemorrhagic shock. D. J. Loegering and F. K. Carr. J. Reticuloendo. Soc. 21: 263-270, 1977.

The time course of changes in circulating opsonic activity and reticuloendothelial (RE) function were determined during the compensatory stages of hemorrhagic shock. Anesthetized rats were hemorrhaged and maintained at 40-45 mmHg arterial blood pressure until the point of initial decompensation (90 min of hypotension). During hypotension plasma opsonic activity immediately decreased 50% and remained near this level while hypotension was maintained. Fifteen min after reinfusion of the shed blood, opsonic activity remained depressed or decreased further. The phagocytic index, determined from the carbon clearance rate, was depressed after reinfusion of the shed blood and followed the same time course as the decrease in opsonic activity. This close temporal relationship between these 2 parameters further supports the concept that a deficiency of circulating opsonic activity mediates the RE system depression during hemorrhagic shock.

30. The effect of coronary perfusion pressure on recovery of myocardial function following normothermic ischemia. E. P. Todd, J. K. Koster, J. R. Utley, C. C. Wachtel, J. C. Collins, E. A. Spaw, and W. G. Marshall. J. Surg. Res. 22: 667-670, 1977.

This report explores the use of increased coronary perfusion pressure immediately following anoxic arrest during cardiopulmonary bypass as an aid in restoring function to a myocardium which has been significantly depressed by ischemia. In this study, the effect of increasing coronary artery perfusion pressure to between 95 and 120 mmHg for 30 min after a 45-min period of normothermic ischemic cardioplegia has been determined. Both myocardial contractility and compliance were significantly improved when compared to a group of animals in which systemic pressure and thus coronary perfusion pressure was maintained between 50 and 70 mmHg.

The approach used in the study present here, of partial aortic obstruction distal to the arterial line of the pump oxygenator, has allowed consistent elevation of coronary perfusion pressure to any desired level without significant alteration in systemic arterial pressure. The data suggest that clinical evaluation of this technique is warranted.

31. Pulmonary wedge catheterization during positive end-expiratory pressure ventilation in the dog. R. Roy, S. R. Powers, Jr., P. J. Feustel, and R. E. Dutton. Anesthesiology 46: 385-390, 1977.

In 10 supine anesthetized dogs, recordings of left atrial (LA) and pulmonary-artery wedge (PW) pressures were simultaneously obtained at several levels of positive end-expiratory pressure (PEEP) ventilation with the thorax either open or closed. Lateral roentgenograms were taken to determine the relative vertical positions of the LA and PW catheter tips. When the wedge catheter tip was vertically above the left atrial catheter tip, mean PW followed airway pressure at PEEP of more than 5 cm H<sub>2</sub>O. For PEEP 5 cm H<sub>2</sub>O or less, and for PW catheter tip positions vertically below the LA catheter tip at all levels of PEEP, mean wedge catheter pressure was close to left atrial pressure. Thus, it appears that LA pressure can best be estimated by PW catheter positions vertically below the left atrium during positive end-expiratory pressure ventilation.

32. The relationship of heparin source to the incidence of delayed hemorrhage. W. W. Abbott, D. F. Warnock, and W. G. Austen. J. Surg. Res. 22: 593-597, 1977.

The incidence of delayed hemorrhage after systemic heparin has been found to vary depending on the origin of the heparin. Delayed hemorrhage occurred with a significantly higher frequency with heparin of intestinal origin compared to that of lung origin. Hemostasis usually remained secure if lung heparin was reversed with protamine, whereas protamine did not influence the results after gut heparin and the incidence of delayed hemorrhage remained very frequent. These differences are probably due to activation of fibrinolysins and suggest circumspection in selecting heparin for clinical use.

33. Liver disease in infants. Part I: Developmental hepatology and mechanisms of liver dysfunction. J. M. Andres, R. K. Mathis, and W. A. Walker. J. Ped. 90: 686-697, 1977.

This review updates and consolidates our understanding of the current concepts of hepatic development (morphologic and functional) and uses this information to help explain clinical manifestations of hepatic disease states in infancy. It is impossible to cover comprehensively all aspects of liver disease in infants. Instead, the authors intend to provide a background for a reasonable and expedient approach to the diagnosis and appropriate management of patients with specific hepatic conditions.

34. Anwendung von ketamin bei lebergeschädigten patienten. (The use of ketamine in patients with liver damage.) D. Schaps and E. Hauenschild. Anaesthesia 26: 172-175, 1977.

Continuous ketamine drip anaesthesia was used in 151 patients with liver disease. The anaesthetic management is described and changes in serum enzymes and bilirubin are reported. Results indicate that ketamine does not impair hepatacellular function.

35. Effect of corticosteroids on lymphocyte activation. D. Tak Yan Yu. Blood 49: 873-881, 1977.

Human peripheral blood lymphocytes were stimulated by concanavalin A, sodium periodate, and neuraminidase plus galactose oxidase. Response to mitogens was measured by the amount of tritiated thymidine incorporated as well as the percent of "giant sheep red blood cell rosettes" generated. The thymidine incorporation was diminished by the absence of monocytes or the presence of corticosteroids. The percent of giant rosettes generated was not influenced by either change. This finding suggested that considerable lymphocyte activation could still take place in the presence of corticosteroids. When subjects received 60 mg of prednisone, they developed lymphopenia 5 hr later. The circulating lymphocytes at that time responded less well to mitogen stimulation when measured by both thymidine incorporation and percent giant rosettes, suggesting a selective sequestration of mitogen-responsive lymphocytes outside the circulatory compartment.

36. Lipid A as the biologically active moiety in bacterial endotoxin (LPS)-initiated generation of procoagulant activity by peripheral blood leukocytes. J. Niemetz and D. C. Morrison. Blood 49: 947-956, 1977.

Preparations of rabbit or human leukocytes, when incubated with bacterial endotoxins (lipopolysaccharides, LPS) are stimulated to generate a procoagulant-tissue factor activity (TFA). As LPS has been shown to consist of specific repeating oligosaccharide side chains (O-antigen) linked to a central polysaccharide core region that is, in turn, linked to the lipid region of the molecule (lipid A), we have examined the biochemical requirement of the LPS necessary for generation of TFA. Using preparations of LPS from mutant strains of bacteria, which contain varying amounts of polysaccharide in relation to lipid A, we have demonstrated that activity is associated with the lipid A region of the LPS molecule. These observations have been confirmed using isolated lipid A, which is a potent stimulator of TFA, as well as a native protoplasmic polysaccharide that is both devoid of lipid A and without detectable TFA stimulatory activity. Modification of LPS by treatment with mild alkali abrogated its capacity to stimulate TFA generation. In addition, such altered preparations of LPS partially inhibit the stimulatory effect of native LPS. Similarly, treatment of LPS (or lipid A) with the antibiotic polymyxin B substantially inhibited the stimulatory effect of LPS.

37. Potency and duration of action of glucocorticoids: Effects of hydrocortisone, prednisone and dexamethasone on human pituitary-adrenal function. A. W. Meikle and F. H. Tyler. Am. J. Med. 63: 200-207, 1977.

This study was designed to quantitate the relative potencies of orally administered glucocorticoids and to investigate some of the factors affecting their relative potency in normal subjects. Corticosterone was measured in plasma samples obtained at 8 AM from 8 normal adult subjects, 3 women and 5 men, following oral doses of dexamethasone, prednisone and hydrocortisone on the preceding midnight, at 6 PM and 8 AM. The half-time of disappearance of prednisolone and dexamethasone from plasma and their free concentrations in plasma were also determined. Concentrations of plasma corticosterone and cortisol showed a significant correlation ( $r=0.68$  to  $0.99$ ,  $p<0.05$  to  $0.001$ ) in all subjects before and after dexamethasone therapy. The mean weighted estimates of the relative potency were calculated for each steroid as a function of time: at 8 hrs, hydrocortisone 1, prednisone 3 and dexamethasone 52, and at 14 hrs, hydrocortisone 1, prednisone 5.2 and dexamethasone 154. Their effects extrapolated to zero time, an estimate of their action that is independent of their rate of clearance from plasma, showed the following relative responses: hydrocortisone 1, prednisone 1.05 and dexamethasone 17. Their biologic half-times of effect were from 1.5 to 2.0 times their half-time of disappearance from plasma. A significant correlation ( $p<0.001$ ) was observed between the log of the total and free concentration of unconjugated prednisolone and dexamethasone and the log of the respective doses of prednisone and dexamethasone administered at midnight. Following doses of prednisone and dexamethasone given at midnight, 7 of 8 subjects showed a significant correlation ( $p<0.05$  to  $0.01$ ) between the free plasma level of prednisolone or dexamethasone and the concentration of corticosterone in the plasma sample obtained at 8 AM. The data indicate that relative intrinsic biologic potency and relative rates of disappearance from plasma are two of the most important factors in determining the relative glucocorticoid potency of orally administered glucocorticoids.

38. Delayed hypersensitivity: Indicator of acquired failure of host defenses in sepsis and trauma. J. L. Meakins, J. B. Pietsch, O. Bubenick, R. Kelly, H. Rode, J. Gordon, and L. D. MacLean. Ann. Surg. 186: 241-250, 1977.

Primary failure of host defense mechanisms has been associated with increased infection and mortality. Anergy, the failure of delayed hypersensitivity response, has been shown to identify surgical patients at increased risk for sepsis and related mortality. The anergic and relatively anergic patients whose skin tests failed to improve had a mortality rate of 74.4%, whereas those who improved their responses had a mortality rate of 5.1% (P 0.001). This study documents abnormalities of neutrophil chemotaxis, T-lymphocyte rosetting in anergic patients and the effect of autologous serum. These abnormalities may account for the increased infection and mortality rates in anergic patients.

39. Adult respiratory distress syndrome (ARDS), sepsis and extracorporeal membrane oxygenation (ECMO). D. A. Browdie, R. Deane, T. Shinozaki, J. Morgan, J. E. DeMeules, L. H. Coffin, and J. H. Davis. J. Trauma 17: 579-586, 1977.

This report presents data obtained in the care of 830 patients requiring assisted ventilation. When these patients were divided into groups by the severity of their respiratory failure as defined by the duration of ventilatory assistance (>48 hrs, <48 hrs) and level of positive and expiratory pressure (PEEP) required (>5 cm H<sub>2</sub>O, <5 cm H<sub>2</sub>O), it was found that evidence of concurrent bacterial infection was present in the majority of patients with severe respiratory failure. This finding could not be explained by infection acquired after the onset of respiratory failure. In addition, this analysis demonstrated the important association of active pulmonary infection with the occurrence of barotrauma in these patients. Case analysis of patients subjected to extracorporeal membrane oxygenation has led to the suggestion that underlying sepsis in patients failing to respond to conventional ventilatory assistance similarly limits the usefulness of membrane oxygenator support.

40. Effects of methylprednisolone on the physical properties of the human red cell. P. W. Rand, E. Lacombe, N. D. Barker, and G. L. Kallechey. J. Lab. Clin. Med. 89: 1241-1250, 1977.

Prompted by evidence suggesting preserved red cell deformability in cardiac surgical patients pretreated with pharmacologic dosages of methylprednisolone, the authors performed in vitro experiments to examine the ability of similar levels of methylprednisolone and hydrocortisone to modify erythrocyte membrane changes produced by metabolic depletion or membrane-active compounds. Variables measured included cell morphology, blood viscosity, membrane deformability, osmotic fragility, red cell cholesterol, and glycolytic intermediates. In incubated samples, methylprednisolone partially prevented the transition of discs to echinocytes, the rise in whole blood viscosity, the decrease in membrane deformability, and the loss of red cell cholesterol which accompany ATP depletion, but it had no apparent effect on red cell glycolysis. The drug also inhibited esterification of cholesterol in cell-free serum. In unincubated samples to which lysolecithin was added, methylprednisolone partially prevented and reversed morphologic and rheologic responses without affecting membrane cholesterol. Hydrocortisone demonstrated similar properties. Possible mechanisms for these actions are discussed. The concept is advanced that preserved blood fluidity may contribute to the beneficial responses to these drugs in certain clinical conditions.

41. An abnormal response of nude mice to endotoxin. R. N. Moore, K. J. Goodrum, L. J. Berry, and J. R. McGhee. J. Reticuloendo. Soc. 21: 271-278, 1977.

Congenitally athymic nude mice were found to behave abnormally to injections of hydrocortisone and bacterial endotoxin. Hormonal induction of hepatic phosphoenolpyruvate carboxykinase (PEPCK), which is inhibited in endotoxin poisoned conventional mice, was not inhibited by endotoxin in these mutant animals. Serum from Zymosan-stimulated normal mice which had been injected with endotoxin significantly depressed PEPCK induction in the nude mice. Zymosan-induced peritoneal cells taken from conventional animals and injected into the nude animals in a suspension containing endotoxin also inhibited PEPCK induction in these athymic mice. Since the phenotypically normal, heterozygous littermates responded normally to injections of hydrocortisone and endotoxin, the uninhibited induction of PEPCK in endotoxin poisoned nude mice must be a result of the nude mutation. These results further substantiate the existence of an endotoxin induced, glucocorticoid antagonizing factor and suggest that the nude mice do not produce appreciable amounts of the substance in response to endotoxin.

These studies have concentrated on PEPCK inducibility as an indicator of metabolic regulation rather than its role as a gluconeogenic enzyme. It is pertinent to note, however, that in preliminary experiments involving relatively small numbers of animals, an abnormal response to endotoxin is observed in the athymic mice with regards to carbohydrate metabolism. Four hr after an injection of a sublethal dose of endotoxin, liver glycogen and blood glucose levels are not as severely depressed as in conventional mice. These mutant animals may prove to be useful in future investigations of the hypoglycemic effect of endotoxin.

42. The effects of endotoxemia and fluid expansion on gastric hemodynamics and mucosal permeability in the baboon. M. J. Zinner, N. J. Gurll, and D. G. Reynolds. J. Surg. Res. 22: 605-510, 1977.

Upper gastrointestinal bleeding from diffuse acute gastric erosions is a serious complication of sepsis. The effects of sublethal intravenous endotoxin on gastric hemodynamics and mucosal ionic permeability were studied in 8 adult baboons. Each baboon had constrictuion of an internally drained Heidenhain pouch 2 weeks prior to testing. Ionic fluxes were determined by instillation and recovery of an acid test solution (ATS) containing 80 mM HCl and 80 mM NaCl. Four hours of endotoxemia resulted in significant decreases in cardiac output and mucosal blood flow to about one-half of control values. There was a small but insignificant increase in hydrogen back diffusion from  $-58 \pm 26$  to  $-131 \pm 59$   $\mu\text{equiv}/30 \text{ min}/100 \text{ cm}^2$  and no significant change in sodium flux from  $+183 \pm 44$   $\mu\text{equiv}/30 \text{ min}/100 \text{ cm}^2$  with shock. Endotoxic shock resulted in a significant decrease in the transmucosal electrical PD from  $40 \pm 3$  to  $29 \pm 4$  mV with a significant increase in potassium flux from  $6 \pm 2$  to  $11 \pm 3$   $\mu\text{equiv}/30 \text{ min}/100 \text{ cm}^2$ , both indicating mucosal damage. All pouches developed acute superficial erosions. Fluid resuscitation corrected blood flow and cardiac output without significantly changing ionic fluxes or potential difference. In the baboon, endotoxemia and its attendant ischemia in the presence of acid may result in clinically significant stress ulcers without significant increases in gastric mucosal ionic permeability.

43. Prevention of endotoxin-induced changes in oxidative phosphorylation in hepatic mitochondria. R. G. DePalma, M. H. Glickman, P. Hartman, and A. V. Robinson. Surgery 82: 68-73, 1977.

*E. coli* endotoxemia affects hepatic energy linked function by uncoupling oxidation from phosphorylation. This study was done to determine whether a steroid, methylprednisolone sodium succinate (MPS), as well as excess substrate sodium succinate (SS), alters directly the effects of endotoxin on hepatic mitochondria. An assay system using  $\alpha$ -ketoglutarate ( $\alpha$ -Kg) was developed to test this hypothesis. Isolated rat hepatic mitochondria were first incubated in concentrations of MPS, ranging from 2.0 to 6.0 mg/ml. At these concentrations uncoupling identical to that occurring with addition of endotoxin resulted. However, a more dilute solution of MPS, 0.12 mg/ml, permitted normal mitochondrial function. Preincubation of MT in 0.12 mg/ml of MPS, as well as with sodium succinate, prevented endotoxin-induced coupling. Both endotoxin and steroid resulted in increased ATPase activity in the medium. While preincubation with MPS blocks the endotoxin effect, very high steroid concentrations alone are harmful. A direct action of steroids on mitochondria is evident, as well as a weaker protective effect due to excess substrate ( $\alpha$ -Kg + SS). Since mitochondria are probably in direct communication with extracellular fluid, the assay system permits interaction of endotoxin, steroids, and substrates which mimic those which occur *in vivo*. The results of this study account for the previously reported variable effects obtained when steroids have been tested *in vivo*.

44. Filtration leukopheresis granulocyte support for infected neutropenic patients. R. McLennan, J. F. Bishop, and M. G. Whiteside. Med. J. Aust. 1: 477-478, 1977.

A pilot study of granulocyte support for neutropenic infected patients by means of white cells collected from the Amino Celltrifuge at the Peter MacCallum Clinic showed acceptable side effects in donor and recipient, and an encouraging recovery occurred in two out of four patients treated. White cell filtration leukopheresis was introduced at the Alfred Hospital Haematology and Medical Oncology Unit in November 1975, for supportive therapy of all patients with white cell counts below  $500/\text{mm}^3$  who had sustained febrile episodes (temperatures greater than  $38^\circ\text{C}$  for more than 48 hours) while receiving appropriate or empiric parenteral antibiotic therapy. A minimum of four or more daily transfusions was given from group and cross-matched compatible donors until fever lysis, recovery of the neutrophil count to over  $500/\text{mm}^3$  or death. Of 13 patients given white cell support, 12 survived and were discharged from hospital. One patient died having received only one transfusion when he was moribund. The authors believe that white cell filtration leukopheresis cell support is useful when used with parenteral antibiotic therapy for infected neutropenic patients, and it has resulted in a high rate of recovery from life-threatening infection in patients at risk.

45. Effect of endotoxin shock on skeletal muscle cell membrane potential. W. H. Gibson, J. J. Cook, G. Gatipon, and M. E. Moses. Surgery 81: 571-577, 1977.

Transmembrane potential changes were monitored in 21 dogs that were shocked by intravenous injection of Difco purified endotoxin (055:BS). Corresponding serial measurements of electrolyte concentration in plasma and muscle biopsies

were obtained to assess fluid and electrolyte changes. During shock the transmembrane potential was found to become significantly less negative (-55.2 mv) from a control of -87.5 mv ( $p<0.001$ ). A significant efflux of  $K^+$  ( $p<0.02$ ) from the cell was recorded, but intracellular  $Na^+$  and  $Cl^-$  concentration rose. A plausible explanation for the fluid and electrolyte shifts, possibly due to a decrease in the muscle temperature and a resultant decline in metabolism, has been offered.

46. Migration of transfused granulocytes in leukopenic dogs. F. R. Appelbaum, L. Norton, and R. G. Graw, Jr. Blood 49: 483-488, 1977.

Although granulocyte transfusion therapy has been shown to be effective in infected granulocytopenic animals and humans, the relative effectiveness of granulocytes (PMN) harvested by continuous flow centrifugation (CFC) or by continuous flow filtration leukapheresis (FL) remains uncertain. Studies in vitro of morphology and granulocyte functions have suggested cells collected by FL may be damaged. To compare the function *in vivo* of granulocytes collected by different methods, dogs were made granulocytopenic with cyclophosphamide (CYT) and then transfused with granulocytes collected by CFC or FL. The local neutrophil mobilization (LMN) through a standard skin abrasion into a chamber containing a strong chemoattractant, autologous serum, was measured. Greater LMN was found after transfusions of CFC PMN than after transfusions of the same number of FL PMN ( $p<0.0003$ ). This difference persisted even when the dose of FL PMNs was four times greater than that of CFC PMN and when the FL donor was pretreated with steroids ( $p<0.001$ ). These results suggest that during filtration leukapheresis, granulocytes are functionally altered and that their function *in vivo* may be compromised.

47. The effect of prednisolone on leucocyte function in man. A double blind controlled study. J. R. Clarke, R. F. Gagnon, F. M. Gotch, M. R. Heyworth, I.C.M. MacLennan, S. C. Truelove, and C. A. Waller. Clin. Exp. Immunol. 28: 292-301, 1977.

The effect of prednisolone on various immunological parameters was studied in patients with ulcerative colitis in complete remission. The study was designed as a double blind trial in which patients received either prednisolone or a dummy preparation and the following observations were made: (1) The mean lymphocyte count fell from 1738 cells/mm<sup>3</sup> to 501 cells/mm<sup>3</sup> 4 hr after prednisolone was given but by 24 hr was significantly elevated to 2399 cells/mm<sup>3</sup>; thereafter it returned to normal levels. (2) Surface marker assays of lymphocytes forming spontaneous sheep cell (E), Fc (EA), and C3 (EAC) rosettes; and cells bearing surface immunoglobulin fluctuated in approximately the same pattern as the total lymphocyte count. (3) The mitotic response to a submaximal stimulating dose of phytohaemagglutin (PHA) was significantly depressed 4 hr after steroid administration but returned to normal by 24 hr. (4) Spontaneous and PHA-induced lymphocyte mediated cytotoxicity fell significantly by 4 hr and remained depressed to the end of steroid administration. The PHA-induced cytotoxicity was still significantly depressed 7 days after steroid administration was stopped. (5) K-cell cytotoxicity did not follow the general pattern and was only slightly reduced at 4 hr being lowest after 24 hr and still depressed 7 days after cessation of steroid administration. (6) The number of plasma cells in the rectal lamina propria showed no significant change after one week of steroid administration. (7) No significant changes occurred in any

of the above assays, in the control group. (8) Polymorphonuclear leucocyte counts rose sharply by 4 hr in the patients receiving prednisolone. There was also a smaller but significant rise in the control group. They remained elevated for 7 days in the group receiving prednisolone, and subsequently fell to normal levels. The control group had returned to initial levels by 24 hr. (9) No significant difference in the bactericidal capacity of polymorphs or the opsonising capacity of patients' sera was observed at any stage in the study.

48. Bacterial shock. H. Shubin, M. H. Weil, and R. W. Carlson. Am. Heart J. 94: 112-114, 1977.

Bacterial shock due to gram-negative bacillus is best managed by prompt control of the infection with appropriate antibiotics and surgical drainage or excision. Corticosteroids for purposes of controlling systemic reactions to bacteria and their toxins constitute adjunctive therapy. Volume repletion and respiratory support may be of the greatest importance for temporary support of these critically ill patients. Vasoactive drugs including dopamine and isoproterenol should be used very sparingly and only as very temporary expedients.

49. Corticosteroids and infectious diseases. D. C. Dale and R. G. Petersdorf. Med. Clin. N. A. 57: 1277-1287, 1973.

The value of steroid therapy in the treatment of gram-negative sepsis with hypotension is still debated because adequately controlled studies have not been performed. Furthermore, the techniques for monitoring and supporting patients with gram-negative shock are improving, leading to changing criteria for use of steroids. Although earlier studies did not support the efficacy of steroids in shock, recently enthusiasm has been received for employing them in "massive" doses. In experimental endotoxin shock in dogs survival was improved by cortisol in dosages of 50 mg/kg. Clinical observations of patients in shock indicate that the salutary effects of steroids are probably related to their ability to restore cardiac output and peripheral vascular resistance toward normal. Presumably this is mediated by the antagonism of steroids, in very high doses, to the vasoconstrictive effects of catecholamines.

In contrast to previous studies indicating a mortality rate of approximately 50% in gram-negative shock, recent studies using the equivalent of 2000 to 6000 mg of hydrocortisone per 24 hrs have reported survival rates of 85 to 90% in nonleukemic patients. The inference is made that these improved results are due to the adjunctive effect of steroids and not to improved antibiotic therapy or supportive care. Certainly there is little to indicate that the use of high doses of steroids in gram-negative shock for very brief periods, until the clinical status of the patient is stabilized, will worsen the infection. The risks consist primarily of gastrointestinal bleeding, metabolic abnormalities, particularly hyperglycemia, and acute psychosis.

Shock associated with meningococcemia, the Waterhouse-Friedrickson syndrome, is probably pathophysiologically similar to that accompanying other forms of gram-negative sepsis. Patients with meningococcal infections generally have moderate to marked increase in cortisol production rates. On the other hand, those patients with meningococcemia who die with adrenal hemorrhage frequently have low plasma cortisol levels. For this reason steroid therapy in severe meningococcal infections has a physiologic basis and is frequently recommended. It is not known, however, if this form of treatment is effective.

50. Does age affect glucose tolerance? G. M. Reaven. Geriatrics 32: 51-54, 1977.

Although its various aspects are still debated, decreased glucose tolerance appears to be a reality of aging. The per-decade increase in plasma glucose levels is moderate, however--about 2 mg/100 ml in fasting levels and 4 mg/100 ml in postprandial levels. The associated hyperinsulinemia usually accompanying the hyperglycemia also suggests a loss of normal insulin sensitivity with aging. Whether these changes are age-related or result from other phenomena is unclear. If these changes are clinically significant, it's because they would seem to accelerate progression of cardiovascular disease by modulating lipoprotein levels. Therapeutic intervention should be aimed at preventing weight gain, developing a regular exercise program, decreasing dietary carbohydrate, and modifying other risk factors such as hypertension and smoking.

51. Effects of exogenous estrogen on  $pO_2$  and experimental endotoxemia in sheep. G. Crenshaw, Jr., and R. Cefalo. Am. J. Obstet. Gynec. 120: 678-689, 1974.

Parenterally administered estrone and estradiol produce a rapid rise (within 15 minutes) in arterial blood  $pO_2$  (8 mm Hg) in oophorectomized sheep. No changes in arterial blood pH or  $CO_2$  content occur. The effect is not blocked by progesterone but is blocked by the antiestrogen MER-25. It is proposed that this effect is the result of decreased physiologic shunting of blood across the pulmonary circulation. Because of the observation that estrogens elevate the arterial  $pO_2$ , an attempt was made to reverse the pulmonary effects of E. coli endotoxin infusion in sheep by the administration of estrogen. Infusions of conjugated equine estrogens (Premarin) reverse the pulmonary artery hypertension and hypoxia and the clinical signs of respiratory distress seen after infusion of E. coli endotoxin.

52. Effect of bradykinin on muscular glucose uptake in man. G. Dietze and M. Wicklmayr. Klin. Wschr. 55: 357-358, 1977.

Glucose metabolism of the human forearm was studied in 4 healthy volunteers by monitoring arterial deepvenous glucose concentration differences and by the determination of muscle blood flow, using  $^{133}Xenon$  as a tracer, during 25 min intrabrachial -arterial infusion of bradykinin (13.3 ng/min). During the infusion of the kinin the forearms glucose uptake rose continuously from  $0.64 \pm 0.11 \mu\text{moles}$  up to  $1.68 \pm 0.22 \mu\text{moles}$  per 100 g X min after 25 min of the infusion ( $p < 0.005$ ). The enhancement of glucose uptake was partly due to the prompt small acceleration of muscle blood flow and partly to the continuously increasing glucose extraction of the forearm. From these data it is evident that besides insulin there is another physiological agent able to enhance glucose entry into the muscle cell.

53. The predisposition to infection following hemorrhagic shock. B. C. Esrig, L. Frazee, S. F. Stephenson, H. C. Polk, Jr., R. L. Fulton, and C. E. Jones. Surg. Gynec. Obstet. 144: 915-917, 1977.

A better understanding of the effects of hemorrhagic shock has led to improved resuscitation in the early treatment of severe injury. Survival of the severely injured patient, presumably in a state of shock, is still limited by the ability of that patient to resist infection. The biologic mechanisms responsible for infection following trauma are incompletely delineated. For example, whether or not hemorrhagic shock as well as its resuscitation predispose to infection is not known. In most experiments suggesting altered host defenses following shock, animals have not been studied that were resus-

citated from hemorrhagic shock. This experiment was undertaken to determine if the animal resuscitated from hemorrhagic shock is more susceptible to infection than the animal not in a state of shock.

Subsequent life threatening gram-negative infection in patients successfully resuscitated from hemorrhagic shock is becoming increasingly common. Following hemorrhagic shock and resuscitation, Sprague-Dawley rats were given Escherichia coli intraperitoneally to simulate the clinical setting in which peritoneal contamination and hypovolemic shock occur concurrently. A sub-lethal dosage of bacteria resulted in a 100% mortality. This suggests that hemorrhagic shock, even when treated promptly and effectively, predisposes to infection.

54. Renal blood flow, afferent vascular resistance, and estimated glomerular capillary pressure in the nonexposed rat kidney. I. Ishikawa and N. K. Hollenberg. Circ. Res. 41: 67-73, 1977.

Much of the detailed understanding of renal function has come from studies, such as micropuncture, which require exposure of the kidney. In this study we have utilized a new method for assessing afferent arteriolar resistance *in vivo* to assess the influence of renal exposure on renal blood flow and preglomerular resistance in the rat. Exposure of the kidney did not reduce arterial pressure ( $111 \pm 5.4$  vs  $110 \pm 5.5$  mmHg), but did reduce cardiac output ( $298 \pm 32$  vs  $235 \pm 6$  ml/kg per min;  $p < 0.02$ ), and renal blood flow in the exposed kidney ( $5.9 \pm 0.26$  vs  $4.55 \pm 0.19$  ml/g per min;  $p < 0.001$ ). Afferent arteriolar resistance, estimated from the size of microspheres reaching the glomeruli, was increased more strikingly (40%) than total renal resistance (29%), suggesting a quantitatively important influence of the surgery on glomerular capillary pressure. Equations, developed to allow the calculation of glomerular capillary pressure, suggested that glomerular capillary pressure was in the range of 50-60 mmHg in the unexposed kidney, and fell to 45 mmHg in response to trauma. The authors conclude that the surgery required to expose the kidney reduces renal blood flow and has a quantitatively important influence on glomerular capillary pressure--a response which must be considered when interpreting experiments which require surgery. The reduction in flow and capillary pressure may well be a useful part of the renal response to volume deficits and trauma.

55. Changes in humoral components of host defense following burn trauma. A. B. Bjornson, W. A. Altemeier, and H. S. Bjornson. Ann. Surg. 186: 88-96, 1977.

Serum opsonic activity for E. coli 075, conversion of C3 by inulin, total hemolytic complement ( $CH_{50}$ ), levels of native C3, factor B, C3b inactivator (KAF), properdin (P), and immunoglobulins (Ig) were determined in 14 patients with burns involving 13% to 91% body surface during 6-8 weeks postburn. In the 21 uninfected patients, levels of IgG and IgA were reduced during the first 10 days postburn, and decreased concentrations of P and IgM were demonstrated from 3-6 weeks postburn. C3 conversion was reduced from 10 days to 6 weeks postburn. Levels of C3, factor B, and KAF were normal or elevated for the entire study period. No difference in the occurrence of humoral abnormalities was noted in patients with burns caused by flame, immersion scald, or acid contact. Reduction in C3 conversion and P concentration were the only abnormalities which correlated with increasing burn size. Bacteremia and/or fungemia was documented in the other two patients. In one of these patients, reduction in  $CH_{50}$  occurred during septicemia due to S. aureus,

and in the other, reduction in all measurements of complement was associated with candidemia and Pseudomonas septicemia and occurred prior to the development of shock. Serum opsonic activity was only reduced significantly during sepsis, suggesting that this abnormality occurred as a result rather than a cause of infection. These results indicate that consumption of components of the classical and/or alternative pathways of complement activation may be an important mechanism by which infection is perpetuated in the burn patient. They also emphasize the importance of the clinical management of the burn patient in preventing the development of septic complications.

56. Studies on digitalis-induced arrhythmias in glucose- and insulin-induced hypokalemia. R. J. Hall, A. Gelbert, M. Silverman, and R. H. Goldman. J. Pharmacol. Exptl. Ther. 201: 711-722, 1977.

The effect of hypokalemia, produced by glucose and insulin (GI) infusion, on the time taken for digoxin infusion (0.0024 mg/kg/min) to produce toxicity (ventricular tachycardia), and also on left ventricular microsomal  $\text{Na}^+$ ,  $\text{K}^+$ -adenosine triphosphatase ( $\text{Na}^+$ ,  $\text{K}^+$ -ATPase) inhibition at toxicity and myocardial digoxin uptake, was studied in anesthetized dogs. Normokalemic control groups received either saline or GI and potassium infusion. The mean plasma  $\text{K}^+$  during digoxin infusion in hypokalemic animals was  $2.28 \pm 0.11$  mEq/l and they took  $44.9 \pm 3.0$  minutes to reach toxicity; this was significantly less than in either the saline ( $54.8 \pm 3.6$  min; mean plasma  $\text{K}^+$   $3.20 \pm 0.08$  mEq/l) or GI and potassium ( $68.9 \pm 3.0$  min; mean plasma  $\text{K}^+$   $3.92 \pm 0.20$ ) control groups. Our results suggest that  $\text{Na}^+$ ,  $\text{K}^+$ -ATPase inhibition is an important determinant of digitalis toxicity, since inhibition was the same in both normokalemic control groups at toxicity, although plasma  $\text{K}^+$  and time to toxicity were significantly different. Hypokalemic animals, in contrast, although showing more myocardial digoxin uptake and  $\text{Na}^+$ ,  $\text{K}^+$ -ATPase inhibition after a given period of digoxin infusion than glucose, insulin and potassium animals, had significantly less  $\text{Na}^+$ ,  $\text{K}^+$ -ATPase inhibition than either normokalemic group at toxicity. This suggests that more rapid  $\text{Na}^+$ ,  $\text{K}^+$ -ATPase inhibition, combined with independent membrane effects of hypokalemia, causes toxicity to occur earlier and at lower levels of  $\text{Na}^+$ ,  $\text{K}^+$ -ATPase inhibition in hypokalemia than in normokalemia.

57. Effects of methylprednisolone on cardiac lymph in acute myocardial ischemia in dogs. M. Ali, A. Ellis, and G. Glick. Am. J. Physiol. 232: H602-H607, 1977.

It has been proposed that administration of pharmacologic doses of glucocorticoids may be beneficial in the setting of acute myocardial ischemia because of their ability to stabilize lysosomal membranes and thereby to prevent the leakage of proteolytic enzymes into the cytoplasm and interstitium. We collected cardiac lymph in anesthetized open-chest dogs in successive 2-hr periods and used acid phosphatase as our marker lysosomal enzyme. In group 1 ( $n=5$ ), we studied the effect of time alone. In these dogs, the total amount of acid phosphatase decreased ( $p < 0.05$ ). In group 2 ( $n=5$ ), methylprednisolone, 30 mg/kg iv, was given. This drug did not change any variable we measured. Ligation of the circumflex coronary artery in group 3 ( $n=7$ ), produced a significant increase ( $p < 0.05$ ) in the amount of acid phosphatase drained from the heart compared to group 1. In the dogs of group 4 ( $n=5$ ), methylprednisolone did not reduce, and may have augmented, the total amount of acid phosphatase draining from the heart. Thus glucocorticoids do not appear to reduce the amount of acid phosphatase released by the ischemic myocardium into the cardiac lymph.

58. Interaction of transcapillary Starling forces in the isolated dog forelimb. R. A. Brace and A. C. Guyton. Am. J. Physiol. 233: H136-H140, 1977.

Three of the four Starling forces were measured in the intact dog forelimb after anesthetization and all four of the Starling forces were measured in the same forelimb which was surgically isolated yet innervated. In the isolated forelimb, isogravimetric capillary pressure ( $P_{ci}$ ) averaged 15.6 mmHg; colloid osmotic pressure of the plasma proteins ( $II_p$ ) averaged 19.9 mmHg; mean interstitial fluid pressure ( $P_{if}$ ) was +0.4 mmHg, and the average value of interstitial colloid osmotic pressure ( $II_{if}$ ) was 4.9 mmHg. Thus the net imbalance in the Starling forces, i.e.,  $P_{ci} - P_{if}$  - ( $II_p - II_{if}$ ) averaged 0.3 mmHg. Furthermore, the value of  $II_{if}$  was consistently decreased after isolation (average decrease of 1.2 mmHg) while  $P_{if}$  was always increased following isolation (average increase of 4.3 mmHg). In addition, it was found that if the forelimb was denervated during isolation, then  $P_{if}$  was increased by an average of 2 mmHg above  $P_{if}$  in the innervated, isolated forelimb. In summary, these studies show that the differences between the intact and isolated forelimb are that  $P_{ci}$  averages 10-11 mmHg in the intact forelimb and 15-16 mmHg in the isolated innervated forelimb while interstitial fluid pressure is negative in the intact limb and positive in the isolated limb.

59. Determinants of isogravimetric capillary pressure in the isolated dog hindlimb. R. A. Brace, A. C. Guyton, and A. E. Taylor. Am. J. Physiol. 233: H130-135, 1977.

The hindlimb of the dog was rapidly isolated and carefully perfused in an attempt to prevent transcapillary fluid shifts into the interstitium which may occur during normal surgical isolation and perfusion. In the control preparation before weight was allowed to increase, isogravimetric capillary pressure ( $P_{ci}$ ) averaged 8 mmHg lower than colloid osmotic pressure of the plasma ( $II_p$ ). As the weight of the leg was increased,  $P_{ci}$  increased and  $II_p - P_{ci}$  decreased. When weight was increased by 5.8%,  $II_p - P_{ci}$  averaged 3 mmHg; with a 9.8% increase in weight,  $II_p - P_{ci}$  averaged 1.3 mmHg. The calculated value of compliance of the interstitial space averaged 0.50 ml/mmHg per 100 g of tissue and increased approximately 10-fold as the weight of the leg was increased. Since  $II_p - P_{ci}$  has always been reported to be approximately 2 mmHg when the hindleg was isolated with standard surgical techniques, these data suggest that the procedures normally used to isolate and perfuse the hindlimb caused the weight of the limb to increase by 6% or more before  $P_{ci}$  was determined. Furthermore, it appears that most of the variation in the reported value of  $P_{ci}$  is due to variation in the value of  $II_p$  since  $II_p - P_{ci}$  has always been reported to be very close to 2 mmHg in the isolated hindlimb.

60. Mechanism of anti-complementary activity of corticosteroids *in vivo*: Possible relevance in endotoxin shock. J. T. O'Flaherty, P. R. Craddock, and H. S. Jacob. Proc. Soc. Exptl. Biol. Med. 154: 206-209, 1977.

Corticosteroids protect animals from potentially lethal doses of endotoxin, but the mechanism for this protection remains as controversial as the mechanism for the toxicity of endotoxin itself. Recent evidence suggests that complement activation may be involved. The effects of several corticosteroids on the sudden neutropenia which occurs in animals exposed to activated complement components were studied. Solu-Medrol and Solu-Cortef in high concentrations inhibited such neutropenia but only if present before or during the period of complement activation; Decadron was much less efficient. The observed dose and temporal relationships are strikingly similar to those

noted in previous studies of corticosteroid protection from endotoxin shock, suggesting that complement-mediated alterations in neutrophils may be critical in this entity.

61. Adverse cardiodynamic effects of vasopressin not avoided by selective intra-arterial administration. K. R. Sirinek, N. R. Thomford, and W. G. Pace. Surgery 81: 723-728, 1977.

In this study, lysine-vasopressin, administered either as a continuous, intravenous infusion (1 unit/kg/hr) or as a selective infusion into the superior mesenteric artery (0.2 unit/min), produced equal (+25%), significant ( $p<0.05$ ), and sustained (60 min) reductions in portal pressure. Compared to intravenous administration, selective intra-arterial infusion of vasopressin resulted in similar reductions in cardiac output (+38%), myocardial contractility (+23%), and coronary flow (+53%). Since these adverse cardiodynamic effects were not avoided by selective intra-arterial infusion, it would appear that administration of vasopressin as a continuous infusion through a peripheral vein remains the most rapid and practical method of administering the drug.

62. Haemorrhagic complications of heparin therapy. M. J. Mant, B. D. O'Brien, K. L. Thong, G. W. Hammond, R. V. Birtwhistle, and M. G. Grace. Lancet 1: 1133-1135, 1977.

In a prospective trial 76 patients with venous thromboembolism have received intermittent constant-dosage heparin or continuously infused heparin with laboratory control. Frequencies of bleeding were similar in both groups. 32% of all patients bled, 13% severely. Retroperitoneal hemorrhage occurred in 5 patients. Major spontaneous bleeding was commoner in older patients and minor spontaneous bleeding in women. Bleeding was uncommon during the first 2 days of treatment, and its daily frequency was relatively constant thereafter. 21% of surgical wounds and 7% of arterial and venous puncture sites bled. These preliminary results illustrate the hazards of heparin therapy and suggest that bleeding complications are more closely related to duration of therapy, age, sex, and surgical trauma than to method of administration.

63. Positive inotropic response to inosine in the in situ canine heart. C. E. Jones, J. X. Thomas, Jr., M. D. Devous, C. P. Norris, and E. E. Smith. Am. J. Physiol. 233: H438-H443, 1977.

Effects of inosine on left ventricular contractile force, circumflex blood flow, heart rate, and arterial pressure were investigated in mongrel dogs. Infusion of 50 ml of 10, 25, or 50 mM inosine into the right atrium over 5 min produced arterial blood inosine concentrations of 20-120 M. Infusion of inosine concentrations of 10 mM or greater produced statistically significant increases in contractile force and circumflex blood flow ( $p<0.05$ ). The increases in contractile force and circumflex blood flow caused by 50 mM inosine were approximately 40% and 110%, respectively. No statistically significant increases in heart rate or arterial pressure were observed during infusion of inosine at any concentration. Administration of propranolol (2 mg/kg) in no way altered the effects of inosine on contractile force or circumflex blood flow. Thus, the present study suggests that inosine in concentrations which may be produced in the myocardium during stressful conditions causes a substantial effect on the inotropic state of the heart and that the effects of inosine are not mediated through adrenergic mechanisms.

64. The possible roles of histamine, 5-hydroxytryptamine and prostaglandin F<sub>2a</sub> as mediators of the acute pulmonary effects of endotoxin. J. R. Parratt and R. M. Sturgess. Br. J. Pharmac. 60: 209-219, 1977.

1. In an attempt to investigate the possible role of released vasoactive substances in mediating the pulmonary pressor responses to E. coli endotoxin, cats were pretreated with histamine, 5-hydroxytryptamine (5-HT) or prostaglandin antagonists, with a histamine depleting agent (compound 48/80) or with an inhibitor of prostaglandin synthetase (sodium meclofenamate).
2. The administration of endotoxin (2 mg/kg) resulted in a rapidly developing pulmonary hypertension (pressure twice normal after 2-3 min), increases in right atrial and intratracheal pressures, systemic hypotension and bradycardia. These effects were unaffected by methysergide in a dose sufficient to prevent the effects of intravenously administered 5-HT.
3. Endotoxin responses were also unaffected by a combination of mepyramine and burimamide in doses sufficient to reduce markedly the effects of intravenously-administered histamine. In cats pretreated (chronically or acutely) with compound 48/80, endotoxin induced a transient pulmonary pressor response which was not maintained.
4. The pulmonary and systemic responses to endotoxin were prevented by the prior administration of the prostaglandin antagonist, polyphloretin phosphate and by pretreatment with the prostaglandin synthetase inhibitor, sodium meclofenamate.
5. It is concluded that a pulmonary vasoconstrictor prostaglandin is involved in the acute response to endotoxin in the cat.

65. Feline endotoxin shock: Effects of methylprednisolone on kininogen-depletion, on the pulmonary circulation and on survival. N. Al-Kaisi, J. R. Parratt, H. H. Siddiqui, and I. J. Zeitlin. Br. J. Pharmac. 60: 471-476, 1977.

1. Escherichia coli endotoxin, administered intravenously in a dose of 2 mg/kg to pentobarbitone-anaesthetized, artificially ventilated cats resulted in pulmonary hypertension, systemic hypotension and an immediate (1-2 min) 30-40% reduction in plasma kininogen, an effect which probably indicates a release of plasma kinins.
2. Methylprednisolone (30 mg/kg), when administered 30 min before endotoxin, did not influence the endotoxin-induced pulmonary hypertension or systemic hypotension but completely prevented the depletion of plasma kininogen.
3. In spontaneously breathing cats, methylprednisolone, administered 30 min after endotoxin, caused a rapid repletion of kininogen and prolonged survival (47% at 6 h compared to 10% in the endotoxin-alone animals). Methylprednisolone did not appear to influence lactate production or the hyperventilation observed during the delayed endotoxin shock phase.
4. It is concluded that methylprednisolone does not prevent the release, by endotoxin, of a pulmonary vasoconstrictor prostaglandin, or its effects, but that perhaps by preventing kinin release it may reduce endotoxin-induced capillary leakage.

66. The clinical pharmacology of methylprednisolone sodium phosphate. I. Intramuscular route of administration. E. Novak, A. R. DiSanto, C. E. Seckman, G. Elliott, J. G. Lee, and S. S. Stubbs. J. Clin. Pharmacol. 17: 324-333, 1977.

Intramuscularly administered methylprednisolone sodium phosphate (Medrol Stabisol) in single doses of 40, 80, or 160 mg (methylprednisolone equivalents) had a similar effect as the same doses of methylprednisolone sodium succinate (Solu-Medrol) with regard to eosinophil suppression, elevation of glucose, white blood count differential shifts (lympholytic effect), urinary excretion of sodium and potassium, and localized (pain) and systemic side effects. The average plasma methylprednisolone concentration was approximately 20% higher after the intramuscular administration of methylprednisolone sodium succinate. The differences in plasma methylprednisolone levels produced by the two esters suggest that either hydrolysis of the succinate ester occurs more slowly or the succinate ester distributes more extensively. This difference in plasma level, however, is not reflected in any other pharmacologic evaluation of the two esters, e.g., both eosinophil depression and hyperglycemic response were identical.

No clinically significant changes in the vital signs, standard hematology, and clinical chemistry parameters evaluated were noted after 21 successive doses (q.i.d. for 5 days with one dose in the morning of day 6) of 80 mg methylprednisolone sodium phosphate. An increase was noted in the systolic blood pressure from a pretreatment mean of 113 mmHg to a posttreatment mean of 123 mmHg and an increase in the body weight from a pretreatment mean of 177 pounds to a posttreatment mean of 183 pounds. No signs of adrenal suppression were found as judged by plasma cortisol and ACTH levels. Six (6/12) subjects of the methylprednisolone sodium phosphate group, one (1/12) subject of the vehicle group, and one (1/12) subject of the placebo (sterile saline) group reported the following systemic side effects: gas in stomach, headaches, anorectal itching, and dryness or itching of the skin. No trend was observed for any side effect reported. In these double-blind, randomized studies, single (40, 80, and 160 mg) and multiple (80 mg) intramuscular doses of methylprednisolone sodium phosphate were tolerated in healthy volunteers as well as the same doses of methylprednisolone sodium succinate and similar volumes of vehicle or placebo.

67. Studies on interaction of bacteria, serum factors and polymorphonuclear leukocytes in mothers and newborns. J. H. Dossett, R. C. Williams, Jr., and P. G. Quie. Pediatrics 44: 49-57, 1969.

The bactericidal capacity of newborn infants' whole blood for E. coli was deficient compared to the mothers, and attempts were made to identify cellular or humoral factors responsible for this deficiency. Separated polymorphonuclear leukocytes from newborn infants were found to be similar to polymorphs from mothers in capacity to engulf and kill E. coli and other bacteria so that cellular deficiency was not evident.

Comparison of the serum opsonic capacity of newborn infants' and mothers' sera revealed deficient opsonic capacity for E. coli in newborn sera. The mean opsonic titer for E. coli was 46.7 in mothers and 4.3 in neonates. Serum opsonic titers for Staph. aureus and group B streptococcus were similar. The opsonic capacity for all bacterial species was decreased when the sera were heated or decomplemented with immune complexes indicating the phagocytosis amplifying role of complement.

The newborn-maternal difference in opsonic capacity for E. coli was presumably a result of deficient 19S antibodies, the primary opsonic antibodies for this organisms. Maternal 19S serum fractions alone, however, showed no opsonic capacity for E. coli. Addition of a complement source (newborn serum absorbed with E. coli) revealed the opsonic capacity of these 19S maternal serum fractions for E. coli. Antibodies in 19S serum fractions therefore are efficient opsonins for E. coli; however, complement is necessary to demonstrate their opsonic potential.

68. Mechanical trauma in leukocytes. T. S. Bewitz, T. C. Hung, R. R. Martin, and L. V. McIntire. J. Lab. Clin. Med. 90: 728-736, 1977.

Trauma to blood produced by mechanical stress and surface interaction limits the use of long-term circulatory assist devices and artificial organs. Cardiopulmonary bypass, venovenous perfusion, and hemodialysis may produce profound hematological changes. These include an immediate drop in the number of circulating leukocytes and platelets, followed by a compensatory rise in the number of circulating, immature leukocytes. Erythrocyte fragility increases and hemolysis follows. Some of the functional alterations in leukocytes which follow mechanical or surface trauma are reduced aerobic glycolysis, inhibited chemotactic response, and reduced phagocytic activity.

Leukocytes appear to be as sensitive to mechanical trauma as platelets and probably more susceptible than erythrocytes. The sensitivity of leukocytes to mechanical trauma is important because these cells are commonly implicated in inflammation and allergic response. Leukocyte morphology is altered by relatively low shear stresses, and abnormal cells are commonly sequestered in the lung. Blood flow around the adhered leukocytes produces mechanical stresses that are transmitted to the vascular endothelial cells. Leukocytes which are sequestered in the lung during shock contain mediators for the release of histamine and other vasoactive compounds. Data from the study implicate leukocytes further as a factor in the development of perfusion lung syndrome. Release of the contents of the specific granules may induce further release of vasoactive chemicals from mast cells of the lung and ultimately cause the conditions of shock which are observed.

69. The contribution of splanchnic pooling to endotoxin shock in the dog. W. G. Guntheroth and I. Kawabori. Circ. Res. 41: 467-472, 1977.

To assess the role of splanchnic pooling in the first 4 hrs of endotoxin shock, we measured pressures and flows and injected radiographic contrast material in 56 dogs, while intervening with portacaval shunting, ligation of the portal vein, and splenectomy because these interventions had previously been reported as beneficial. Compared to the intact dogs, those with portacaval shunts had a less precipitous fall in cardiac output and blood pressure following endotoxin, but by 30 min and thereafter there were no substantial differences in the hemodynamics except for a lower portal vein pressure. In addition, there was a greater mortality in the shunted dogs. Ligation of the portal vein in the shunted dogs produced no important differences. Splenectomy alone produced no difference in the intact dogs except for a mild reduction in the peak portal vein pressure after endotoxin, but splenectomy in dogs with shunt and portal ligation was quickly fatal after endotoxin. Radiographic contrast studies demonstrated almost complete

cessation of portal and hepatic vein flow 5 min after endotoxin, with recovery by 1 hr. The course of systemic hemodynamics during endotoxin shock was not altered by portacaval shunting, with or without ligation of the portal vein, and the mortality actually was increased by those interventions. In these experiments, there was no evidence of intravascular pooling (as opposed to extravasation) except for early transient hepatic trapping, which appeared to result from increased venomotor activity.

70. Cardiac output and pulmonary wedge pressure. Use for evaluation of fluid replacement in trauma patients. D. M. Shah, R. D. Browner, R. E. Dutton, J. C. Newell, and S. B. Powers, Jr. Arch. Surg. 112: 1161-1164, 1977.

Cardiac output and pulmonary wedge pressure (PWP) were used to evaluate the end point of fluid resuscitation in 20 patients suffering from multiple trauma and shock. Eleven patients received crystalloid resuscitation and 9 patients received colloid resuscitation. Fifteen of 20 patients had an adequate cardiac output at the termination of resuscitation, but only 6 of these patients had a PWP above 10 mmHg. There was no significant correlation between left ventricular stroke work index and PWP in these patients, either at the completion of resuscitation or during the following 3 days. Five patients did not achieve adequate cardiac output and 4 of these patients died, suggesting that cardiac output was the most important criterion for adequate resuscitation. If the goal of fluid resuscitation is to achieve an adequate cardiac output, then PWP was not a reliable guide. Furthermore, using both cardiac output and PWP as a guide to fluid resuscitation of our patients, we found that the type of fluid (crystalloid or colloid) for resuscitation did not influence the course of respiratory distress in these patients up to 3 days following resuscitation.

71. Methods for measuring plasma to blood glucose in the clinic: A short review. W. A. T. Brunton, and I. W. Percy-Robb. Am. Heart J. 94: 533-536, 1977.

It is commonly found that progress in patient care and in laboratory techniques proceed together. Advance in the understanding of factors affecting glucose metabolism and in the care of conditions resulting from abnormal glucose metabolism has led to pressure on the development of rapid methods for measurement of glucose concentration in blood or plasma. These methods have been modified for use by medical or nursing staff to enable them to perform the assays in the clinic or hospital ward without a requirement for the extensive training needed by professional laboratory staff. This article describes the performance of two systems developed for measuring blood or plasma glucose concentrations under these circumstances.

72. Steroids and severe hemorrhagic shock. J. Pinilla and C. J. Wright. Surgery 82: 489-494, 1977.

This study was designed to determine the effect of high-dose steroid therapy on certain hemodynamic and metabolic functions during the treatment of severe hemorrhagic shock. Thirty dogs were bled to a mean arterial pressure of 30 mmHg for 90 min. Resuscitation then was commenced by reinfusion of shed blood and Ringer's lactate. Methylprednisolone (30 mg/kg) was given intravenously immediately before retransfusion to one-half of the animals. Mean arterial pressure, cardiac index, total peripheral resistance, femoral artery blood flow, and muscle capillary blood flow during exercise were measured before hemorrhage and at intervals after resuscitation. Total oxygen uptake, hindlimb oxygen uptake, and lactate production were calculated from the femoral blood flow and appropriate arterial and venous concentrations.

The mean survival time was similar in both groups (with steroid,  $28.1 \pm 13.1$  hr; without,  $30.1 \pm 12.3$  hrs). Mean arterial pressure and total peripheral resistance were lower in the group receiving steroids ( $p < 0.05$ ). There was no significant difference between the groups in cardiac output, cardiac index, femoral artery blood flow, muscle blood flow, limb oxygen uptake, and lactate production. The results do not demonstrate any advantage of steroid therapy in the management of severe hemorrhagic shock in this model.

73. Effect of platelet antiserum on the activation of intravascular coagulation by endotoxin. W. Kramer and G. Muller-Berghaus. Thrombosis Res. 10: 47-70, 1977.

The importance of platelets in the activation of endotoxin-induced intravascular coagulation was investigated in rabbits made severely thrombocytopenic by an intravenous injection of platelet antiserum. Goat antiserum removed more than 98% of the circulating platelets. If two doses of endotoxin were injected intravenously into thrombocytopenic rabbits, renal glomerular microclots still occurred, but coagulation analysis showed a definite reduction of intravascular coagulation. The occurrence of microclots after endotoxin injection into thrombocytopenic rabbits could be prevented by continuous infusion of heparin. The treatment of another group of rabbits with the threefold dose of antiserum prevented the occurrence of renal glomerular microclots after endotoxin injection. No correlation between platelet counts prior to the second dose of endotoxin and the occurrence of glomerular microclots could be demonstrated. With this study, the importance of platelets in triggering endotoxin-induced generalized intravascular coagulation becomes doubtful. The effect of platelet antiserum in preventing the occurrence of generalized intravascular coagulation may depend on its influence on other mechanisms important in activating intravascular coagulation by endotoxin.

74. The role of granulocytes in the activation of intravascular coagulation and the precipitation of soluble fibrin by endotoxin. G. Muller-Berghaus and T. Eckhardt. Blood 45: 631-641, 1975.

This study examines the role of neutrophils (PMN) in the pathogenesis of endotoxin-induced microclot formation. It is intended to clarify whether granulocytes are involved in endotoxin-induced activation of intravascular coagulation (generation of soluble fibrin) and/or in endotoxin-induced precipitation of soluble fibrin. Precipitation of soluble fibrin was achieved by injection of endotoxin into anesthetized rabbits with circulating soluble fibrin (first model). Activation of intravascular coagulation was elicited by two intravenous injections of endotoxin into rabbits (second model). Seventy-two and 96 hours after injection of nitrogen mustard, leukopenic rabbits had PMN counts between 0 and 50 cells per  $\mu$ l. Neutropenia did not prevent the occurrence of glomerular microclots after infusion of anesthetized and injection of endotoxin (first model). Neutropenia influenced neither the decrease in mean fibrinogen concentrations nor the drop in mean platelet counts after anesthetized and endotoxin administration. In contrast to the first model, neutropenia prevented the occurrence of glomerular microclots and of circulating soluble fibrin after two injections of endotoxin (second model). It did not, however, protect rabbits from the decrease in mean platelet counts after endotoxin administration. These data indicate that granulocytes are involved in endotoxin-induced activation of intravascular coagulation and the production of soluble fibrin but are not essential to endotoxin-induced precipitation of soluble fibrin.

75. Indicators of intensive care in critically ill patients. D. J. Cullen, L. C. Ferrara, J. Gilbert, B. A. Briggs, and P. F. Walker. Crit. Care Med. 5: 173-179, 1977.

To define severity of illness objectively and to justify further the need for intensive care, we have analyzed measurable objective data points (indicators) in 226 consecutive critically ill Class IV patients. The indicators include (1)  $\text{PaO}_2$  ( $\text{FIO}_2$ , 1.0), (2) platelet count, (3) cardiac index, (4) BUN, (5) creatinine, (6) acute renal failure, (7) peritoneal or hemodialysis, (8) continuous infusion of antiarrhythmia therapy, (9) base deficit  $> 10 \text{ mEq/liter}$ , (10) state of consciousness, and (11) unexpected cardiac arrest.

Most indicators were significantly worse in patients who ultimately died within one year than in patients who survived with a successful recovery. An indicator profile could be derived for each disease process category, since different indicators applied to different diseases. The indicators were not markedly affected by age. Standard discriminant analysis predicted a group of patients who would not survive and documented that acute renal failure was a primary predictor of death.

76. Acute circulatory failure (shock) associated with cardiogenic pulmonary edema. M. H. Weil and R. J. Henning. Crit. Care Med. 5: 215-219, 1977.

Our findings confirm that acute pulmonary edema, when caused by left ventricular failure, represents a form of acute perfusion failure (shock) with metabolic acidemia, lactacidemia, and a reduction in forward blood flow. It is associated with a marked increase in peripheral resistance and an increase in venous capacitance. Most importantly, acute pulmonary edema is associated with a reduction in the intravascular blood volume.

Acute pulmonary edema is not fundamentally different from other types of shock in which the shock state is initiated by one primary defect, and during the course of its progression, other primary mechanisms are called into action. In the instance of acute cardiogenic edema, the primary defect is cardiac pump failure and the secondary defects include hypovolemia and distributive defects associated with arterial vasoconstriction and expanded venous capacitance.

Furosemide reverses acute pulmonary edema by increasing rather than decreasing intravascular blood volume with consequent improvement in the distributive and hypovolemic defects. Under extreme conditions, the volume defect in acute pulmonary edema may be so great that the patient presents with primary hypovolemia. The utilization of volume repletion is warranted under these circumstances.

77. Effect of leukocytic endogenous mediators on endocrine pancreas secretory responses. D. T. George, F. B. Abeles, C. A. Mapes, P. Z. Sobocinski, T. V. Zenser, and M. C. Powanda. Am. J. Physiol. 233: E240-E245, 1977.

Crude mediators from stimulated rabbit peritoneal leukocytes (LEM) engender numerous physiologic alterations in rats, which are similar to those observed during infection. One hour after the intraperitoneal injection of crude LEM, plasma insulin and glucagon concentrations are elevated; at 2 hr the hormonal alterations are manifested by a 30% increase in hepatic cyclic adenosine 3',5'-monophosphate (cAMP), glycogen depression, and uptake of  $^{14}\text{C}$ -labeled nonmetabolizable amino acid analogues (AA). Plasma hormone concentrations reach maximum levels by 5 hr and decline by 24 hr. The hepatic concentrations

of AA parallel the insulin and glucagon responses and correlate with the inverse of insulin/glucagon molar ratio. In spite of mobilization of hepatic glycogen evident at 5 hr, plasma glucose concentrations were transiently depressed. Plasma insulin, glucagon, and hepatic AA concentrations were dose dependent. Plasma insulin and glucagon responses to crude LEM may explain increases in hepatic cAMP, uptake of AA, and glycogenolysis as well as hypoglycemia. These data partially characterize the role of crude LEM, provide an explanation for the stimuli-inducing hyperglucagonemia and hyperinsulinemia during infection. They implicate the endocrine pancreas as a factor regulating the host's metabolic response to infection.

78. Relation between lowered colloid osmotic pressure, respiratory failure, and death. A. S. Tonnesen, J. C. Gabel, and C. A. McLeavey. Crit. Care Med. 5: 239-240, 1977.

Plasma colloid osmotic pressure was measured each day in 84 intensive care unit patients. Probit analysis demonstrated a direct relationship between colloid osmotic pressure (COP) and survival. The COP associated with a 50% survival rate was 15.0 torr. COP was higher in survivors than in nonsurvivors without respiratory failure and in patients who recovered from respiratory failure. We conclude that lowered COP is associated with an elevated mortality rate. However, the relationship to death is not explained by the relationship to respiratory failure.

79. Does breast milk protect against septicaemia in the newborn? J. Winberg and G. Wessner. Lancet 1: 1091-1094, 1971.

Newborn babies with onset of probably hematogenous infections between the 4th and 10th day of life were compared with matched controls with regard to early breast-milk consumption. The patient group consumed, before onset of the first suspected symptoms, significantly less breast milk than did the controls. The low consumption was probably due to hypogalactia of the mother. It is suggested that breast milk may offer a certain immunity to the newborn against early infections by bacteria of enteric origin.

80. Effects of corticosteroid therapy on human monocyte function. J. J. Rinehart, A. L. Sagone, S. P. Balcerzak, G. A. Ackerman, and A. F. LoBuglio. New Engl. J. Med. 292: 236-241, 1971.

Since high-dose corticosteroid therapy appears to impair cellular defense mechanisms, this study examined its effect on human monocyte function. Fifteen normal volunteers were studied before and after a 3-day course of prednisone therapy (50 mg every 12 hours for six doses). A transient period of monocytopenia occurred during the first few hours of therapy. Monocyte killing of Staphylococcus aureus was reduced in nine subjects from  $5.6 \pm 0.2$  ( $\pm SE$ )  $\times 10^6$  organisms before to  $1.3 \pm 0.4 \times 10^6$  organisms at completion of therapy ( $p < 0.01$ ). Similarly, killing of Candida tropicalis in 4 subjects fell from  $9.3 \pm 0.6$  to  $0.6 \pm 0.3 \times 10^6$  organisms ( $p < 0.01$ ). Bactericidal activity returned to normal levels 48 hrs after the last dose of prednisone. These same monocyte preparations had normal or increased chemotactic response, phagocytic rate of cryptococci, hexosemonophosphate-shunt responses to phagocytosis and ultrastructural characteristics. This impairment of bactericidal and fungicidal activity during prednisone therapy may contribute to the infectious complications seen in patients receiving comparable doses of corticosteroids.

81. Effect of endotoxin and postendotoxin plasma on in vitro granulopoiesis.  
P. A. Chervenick. J. Lab. Clin. Med. 79: 1014-1020, 1972.

Increased quantities of colony-stimulating factor (CSF), capable of stimulating the in vitro growth of colonies of granulocytes and mononuclear cells from murine marrow was present in the plasma of mice injected with Salmonella typhosa endotoxin. Increased CSF occurred within 30 min after injection as the animals became neutropenic. Peak activity of approximately 600% of control value occurred between 2 to 8 hrs following the injection of either 5.0  $\mu$ g or 50.0  $\mu$ g of endotoxin. Peak activity occurred between 2 to 4 hrs after 5.0  $\mu$ g and then declined to normal levels by 24 hrs. After 50.0  $\mu$ g, peak activity occurred between 4 to 8 hrs and remained slightly above normal after 24 hrs. The addition of endotoxin directly to unstimulated cultures or to cultures stimulated with conditioned medium did not enhance colony growth. Concentrations of endotoxin less than 0.01  $\mu$ g had no effect, while concentrations of 0.1  $\mu$ g or more inhibited colony formation. Incubating endotoxin with normal mouse plasma (NMP) prior to adding it to the cultures did not enhance colony growth. Thus, postendotoxin plasma has marked stimulatory effects on granulocytopoiesis in vitro, which is not due to endotoxin per se or to its interaction with plasma. The relationship of increased CSF to neutropenia suggests that CSF is a neutropoietin and perhaps a physiologic regulator of granulopoiesis.

82. Regional cerebral blood flows in endotoxin shock with methylprednisolone treatment. T. E. Emerson, Jr., and W. J. Bryan. Proc. Soc. Exptl. Biol. Med. 156: 378-381, 1977.

It has previously been shown that total and regional cerebral blood flows are severely decreased during endotoxin shock. The effects of methylprednisolone and volume expansion therapy on the regional cerebral blood flows during endotoxin shock in anesthetized dogs are described. Methylprednisolone (Solu-Medrol), 30 mg/kg, was injected iv 15 min prior to infusion of E. coli endotoxin (1 mg/kg) and hourly ( $\approx$ 8 mg/kg) for 4 hr of shock. Regional cerebral blood flows were determined using the radioactive-labeled particle distribution technique. In contrast to untreated dogs, treated dogs exhibited no change or an increased blood flow in seven regions of the brain at 2 hr of shock; blood flows in the pons, medulla, hypothalamus, thalamus, and pituitary were not significantly different than control at 4 hr of shock. These data suggest that pretreatment with methylprednisolone, combined with supplemental doses and volume expanders, protects the cerebral circulation during endotoxin shock.

83. Blood flow in seven regions of the brain during endotoxin shock in the dog. W. J. Bryan and T. E. Emerson, Jr. Proc. Soc. Exptl. Biol. Med. 156: 205-208, 1977.

This study was performed to determine regional cerebral blood flow during endotoxin shock using the labeled-microsphere particle distribution technique. The labeled microspheres were 15  $\mu$ m in diameter. Twenty-six anesthetized and ventilated dogs were given 2 mg/kg of E. coli endotoxin. Regional flows were determined before endotoxin and at 2 or 4 hr of shock. The percentage decrease in blood flows at 4 hr of shock of the regions sampled were: pons, 39%; medulla, 43%; hypothalamus, 46%; thalamus, 51%; cortex, 51%; cerebellum, 50%; and pituitary, 52%. Regional resistances of the pons, medulla, and hypothalamus were significantly decreased at 2 and 4 hr of shock. On the other hand, resistances of the cerebellum, cortex, thalamus, and pituitary were not significantly different from control values at either time. We conclude that blood flows to all brain regions measured are severely depressed during endotoxin shock.

84. Effects of methylprednisolone on coronary blood flow and myocardial metabolism during cardiopulmonary bypass. J. F. Vinas, J. G. Fewel, F. L. Grover, J. D. Richardson, K. V. Arom, G. E. Webb, and J. K. Trinkle. Surgery 81: 646-652, 1977.

Corticosteroids frequently are used during cardiopulmonary bypass (CPB) to enhance total body perfusion and myocardial preservation. The mechanisms by which steroids might provide protection to the myocardium have not been clearly defined, however. Therefore this study was performed to measure the effects of methylprednisolone (MP) on coronary flow and distribution, and on myocardial metabolism and contractility. Twenty-three dogs underwent 1 hr of total CPB, 80 cc/kg/min at normothermia with beating hearts. Alternate animals received MP, 30 mg/kg. Myocardial blood flow (microspheres technique), myocardial tissue lactate and adenosine triphosphate, lactate extraction, coronary sinus flow (CSF), and coronary vascular resistance (CVR) were measured before, during, and 60 min after bypass. Total coronary flow was significantly higher in the MP group after 10 and 30 min of bypass. Right ventricular flow was higher in the MP group at 10 and 30 min of bypass. Left ventricular flow was higher in the MP group at 10 min of bypass. Septal flow also was higher in the treated group at 10 min of bypass and at 30 min of bypass. CVR after 10 min of bypass was lower in the steroid group. It is concluded that MP increases coronary blood flow and decreases CVR in the empty beating heart during normothermic CPB without altering myocardial metabolism or contractility.

85. Neutrophil function in selected surgical disorders. J. W. Alexander, M. Hegg, and W. A. Altemeier. Ann. Surg. 168: 447-458, 1968.

This investigation was performed to study the importance of the antibacterial function of polymorphonuclear leukocytes as a factor of host defense in patients with selected surgical disorders. A test which provides separate semi-quantitative measurements of the processes of phagocytosis and intracellular killing of bacteria by human neutrophils has been developed and used to evaluate neutrophil function in a variety of surgical disorders. Significant abnormalities have been demonstrated in patients with thermal trauma, physical injury, biliary obstruction, bacterial infection, and immunosuppressive therapy. In patients with thermal burns, the degree of abnormality could be related directly to the extent of injury and had a temporal relationship to the time of injury.

Abnormalities detected by the tests were usually characterized by an increase in the rate of phagocytosis and an impairment of intracellular killing. Operations of the magnitude of a laparotomy were associated with only slight or no abnormalities.

A normal cyclic variation in neutrophil function has been demonstrated in healthy persons, and it appears that this type of variation can be adversely affected by certain types of therapy.

Abnormalities of neutrophil function may be of etiological importance in the development of microbial infections in surgical patients where no other explanation can be found by analysis of other immunological and physiological variables.

86. Dynamics of insulin and glucagon secretions in severely burned patients.  
J. M. Shuck, R. P. Eaton, L. W. Shuck, T. L. Wachtel, and D. S. Schade.  
J. Trauma 17: 706-713, 1977.

The purpose of the present study was to investigate further the role of the catabolic hormone, glucagon, in thermal injury. Are basal concentrations of insulin and glucagon adequate to interpret their interactions, or are dynamic stimulatory tests required? Finally, is it possible to determine which metabolic events are helpful and which are hurtful to the acutely burned patient?

Sequential aminogenic stimulation of glucagon and glucogenic secretion of insulin were studied in six acutely burned patients. Hyperglycemia and glucose intolerance were demonstrated. The abnormal glucagon secretory dynamics were confirmed by supranormal hormone secretion after arginine challenge. Basal insulin levels were elevated in the patients, and were never low after stimulation. These findings, plus the markedly decreased molar insulin:glucagon ratio, confirmed the severe catabolic state of the burned patient. Elevations in basal serum plasma triglyceride and free fatty acid levels in the acutely burned patient may be related to the hyperglucagonemia, in addition to other catabolic hormones.

The following conclusions are suggested:

- 1) Hyperglucagonemia may contribute to hyperglycemia in acutely burned patients.
- 2) Appropriate insulin responses after arginine and glucose infusions were shown in severe stress. The values of insulin were not low, except in relation to glucose and glucagon concentrations.
- 3) Basal hormone determinations only partially reflect the extent of the abnormality in glucagon and insulin dynamics.
- 4) Glucagon may exert its effect on the regulation of carbohydrate and lipid metabolism in concert with other catabolic hormones early in severe thermal injury.

87. Gentamicin intravenous infusion rate: Effect on interstitial fluid concentration. A. J. Kozak, D. N. Gerding, L. R. Peterson, and W. H. Hall.  
Antimicro. Agents Chemother. 12: 606-608, 1977.

A variety of techniques for intravenous gentamicin administration have been described in the literature. They include rapid bolus, with delivery in less than 1 min, slow bolus with delivery in 2.5 to 5 min, and slow continuous infusion over 1 to 2 hr. To assess the possible role of i.v. infusion rate as a determinant of degree and rate of interstitial fluid penetration, six rabbits, each with four intraperitoneal implanted capsules, were studied by crossover design after a single dose of 1.7 mg of gentamicin per kg by either slow 2.5-min i.v. bolus or 30 min i.v. infusion. The mean serum peak antibiotic level after slow bolus was 17.4  $\mu$ g/ml. After 30 min of infusion, mean serum peak was 8.3  $\mu$ g/ml ( $p < 0.025$ ). Slow 2.5-min i.v. bolus administration of gentamicin established higher interstitial fluid levels during the first 2 hr of therapy and may be the preferred mode of delivery when rapid extravascular penetration is desired.

88. Relative hemodynamic effectiveness of whole blood and plasma expanders in burned patients. W. C. Shoemaker, T. Matsuda, and D. State. Surg. Gynec. Obstet. 144: 909-914, 1977.

In a series of nine fatally burned patients, hemodynamic and oxygen transport measurements were made before, during and after 56 administrations of 500 ml of whole blood or colloids and 1,000 ml of crystalloids. To enhance comparability, 30 of these studies were conducted at intervals on the same patient, the patient serving as his own control. The data indicate greater hemodynamic responses to colloids than to whole blood and greater responses to whole blood than to crystalloids when the latter was given at twice the volume as well as at four times the volume of the colloid. The data suggest that, in addition to replenishing salt and water, restoration of hemodynamic and oxygen transport variables may be accomplished by expansion of plasma volume with colloids and whole blood. Adequate nutrition is also needed for the increased metabolic needs of the burned patient. Without supplemental nutrition, high grade plasma proteins and tissue proteins may be expended as energy substrates; the lowering of plasma proteins tends to redistribute water from the plasma to the interstitial phase, which increases further the peripheral edema.

89. Effect of prolonged bacteremia on leukocyte bactericidal function. J. Postel, D. Furtado, and P. R. Schloerb. Surgery 81: 180-183, 1977.

The purpose of this study was to determine, under controlled conditions, the effects of a non-lethal vs. lethal bacteremia upon normal NBF in dogs. To emphasize the dominant role of the NBF, the relative contribution to the reticuloendothelial system (RES) function to blood bacterial clearance is evaluated. Neutrophil bactericidal function (NBF) was studied in dogs during intravenous infusions of *Pseudomonas aeruginosa*. Administration of  $10^6$  bacteria per min over 3 hrs was associated with a bacteremia level of about  $10^3$  organisms/ml of blood without adverse effects on NBF. Infusion of  $10^7$  organisms/min resulted in blood bacterial counts in the upper  $10^4$  range and significantly impaired NBF. To determine the relative contribution of the spleen in bacterial phagocytosis, splenectomies were performed in additional dogs immediately prior to 5-hr infusions of  $10^6$  *Pseudomonas aeruginosa* per min. Results revealed that splenectomy did not influence the blood bacterial clearance. These experimental findings emphasize the dominant role of polymorphonuclear leukocytes in bacterial defense.

90. Phagocytosis in experimental burns. A. Di Maio, D. Di Maio, and L. Jacques. J. Surg. Res. 21: 437-448, 1976.

These experiments were performed in order to determine the capacity of blood leukocytes and macrophages in liver and spleen, in normal and burned rats, to remove and kill intravenously injected *Salmonella typhi murium*. A 10 to 12% intermediate burn produces a profound perturbation of phagocytic activity 12 hr after burn injury. These results are in agreement with numerous clinical observations and emphasize the concept that phagocytosis is the most important and critical determinant in the outcome of infection following a burn injury.

The variations of phagocytic activity have been measured during a 9-day period following experimental burns. The burns are of an intermediate type; necrosis develops within 2 to 4 days after thermal trauma and covers up to 10% of total body surface. Phagocytic activity has been measured in peripheral blood, spleen, and liver by measuring both clearance of bacteria and the

bactericidal index of the macrophages. Shortly after burn trauma, a considerable inactivation of the bactericidal index has been noticed. The decrease of the phagocytic activity of macrophages in the liver and peripheral blood is important but transient; the decrease of the phagocytic activity of splenic macrophages is drastic and persists unimproved for at least 9 days following burn injury.

91. Neutrophil releasing activity in plasma of normal human subjects injected with endotoxin. D. R. Boggs, J. C. Marsh, P. A. Chervenick, G. E. Cartwright, and M. M. Wintrobe. Proc. Soc. Exptl. Biol. Med. 127: 689-693, 1968.

Normal human subjects were injected with endotoxin and their plasma was harvested at various times thereafter. This plasma was later infused into the same subject, to determine if neutrophilia inducing activity was demonstrable in such plasma. Infusion of normal control plasma induced no significant change in total neutrophil concentration and nonsegmented neutrophils tended to decline after such infusions. Plasma collected after injection of endotoxin did not induce a significant change in blood neutrophils as compared to control plasma if obtained at a time when no significant increase in the rate of release had developed in the donor. Postendotoxin plasma, collected when the donor was releasing neutrophils at an abnormally rapid rate, induced a significant increase in both total and nonsegmented neutrophils. Infusion of active postendotoxin plasma induced a more rapid onset of neutrophilia than did endotoxin injection. This observation and the inactivity of certain plasmas which were collected after the same dose of endotoxin yielding active plasma suggested that the activity of postendotoxin plasma was not representative of persistence of the injected endotoxin.

This study, in conjunction with similar studies in other species, suggests that the rate of release of neutrophils from the marrow to the blood may be controlled by a humoral factor.

92. Hyperactivity of neutrophil leukotactic responses during active bacterial infection. H. R. Hill, J. M. Gerrard, N. A. Hogan, and P. G. Quie. J. Clin. Invest. 53: 996-1002, 1974.

The initial inflammatory response to bacterial invasion of the body is critical as a determinant of the outcome of infection. Animal studies have demonstrated that prompt infiltration of phagocytic cells into an area of bacterial invasion is essential if multiplication of the organism is to be suppressed and generalized infection prevented. Leukotaxis, unidirectional movement of leukocytes toward a chemotactic stimulus, is considered to be one of the mechanisms by which phagocytic cells are attracted to an area of bacterial invasion.

To determine if changes in neutrophil leukocyte function occur during active bacterial infection, the neutrophils of 25 patients with active bacterial infection and 25 age-matched controls were compared for leukotactic activity, random mobility, and nitroblue tetrazolium reduction. The neutrophil leukocytes of patients with bacterial infection were hyperactive in unidirectional movement toward a chemotactic stimulus as measured in the leukotactic assay and usually had increased nitroblue tetrazolium reduction. The mean leukotactic index was  $165 \pm 56$  in patients with bacterial infection and  $70 \pm 11$  in controls ( $p < 0.001$ ). After 7-10 days of appropriate therapy with clinical and bacteriological response, leukotactic activity returned to normal values. A hyperactive leukotactic response continued, however, in patients with

persisting bacterial infection. The hyperactive leukotactic response of circulating neutrophils appears to be an early and sensitive event in the inflammatory cycle stimulated by bacterial infection and may aid in the localization of invading bacteria.

93. Artifactual hypoglycemia associated with leukemia. J. B. Field and H. E. Williams. New Engl. J. Med. 265: 946-948, 1961.

Three patients with leukemia were found to have apparent hypoglycemia that was due to continued glycolysis by the large number of leukocytes between the time the blood was drawn and the sugar determination performed despite the presence of sodium fluoride. This phenomenon was seen in patients with both chronic myelogenous and lymphatic leukemia and was related to the total white-cell count rather than the type of white blood cell. This decrease in blood sugar was inhibited by the addition of excess fluoride or storage of the blood in the refrigerator. No such fall in sugar was observed in control patients or in a patient with acute myelogenous leukemia with white-cell counts under 15,000.

94. Glucose and lactate kinetics after endotoxin administration in dogs. R. R. Wolfe, D. Elahi, and J. J. Spitzer. Am. J. Physiol. 232: E180-E185, 1977.

The effects of *E. coli* endotoxin on the glucose and lactate kinetics in dogs by means of the primed constant infusion of [6-<sup>3</sup>H]glucose and Na-L-(+)-[U-<sup>14</sup>C]lactate were studied. The infusion of endotoxin induced a transient hyperglycemic level, followed by a steady fall in plasma glucose to hypoglycemic levels. The rate of appearance ( $R_a$ ) and the rate of disappearance ( $R_d$ ) of glucose were both significantly elevated ( $p < .05$ ) for 150 min after endotoxin, after which neither differed from the preinfusion value. The metabolic clearance rate of glucose was significantly elevated at all times 30 min post-endotoxin. By 30 min postendotoxin,  $R_a$  and  $R_d$  of lactate, plasma lactate concentration, and the percent of glucose turnover originating from lactate were significantly elevated and remained so for the duration of the experiment. The authors concluded that after endotoxin hypoglycemia developed because of an enhanced peripheral uptake of glucose and a failure of the liver to maintain an increased  $R_a$  of glucose. It was also concluded that lactate became an important precursor for gluconeogenesis and an important metabolic substrate.

95. Artificial liver: The effect of ACAC microencapsulated charcoal hemoperfusion on fulminant hepatic failure. E. Chirito, B. Reiter, C. Lister, and T. M. S. Chang. Artif. Org. 1: 76-83, 1977.

Control trials and statistical analysis were carried out to assess the effects of albumin-collodion microencapsulated activated charcoal (ACAC) hemoperfusion on fulminant hepatic coma. A rat model of galactosamine induced fulminant hepatic coma was used. Rats which did not recover died at  $3.0 \pm 0.6$  days after galactosamine injection. Those which survived this period recovered. Forty-eight hours after galactosamine injection, a test group of 21 rats were treated with 1 hr hemoperfusion and compared with an untreated group of 23 rats. 71.4% of the treated group survived as compared to 30.4% of the untreated rats. Statistical analysis (t test) shows a significant increase in recovery for the treated group ( $< 0.01$ ). Biochemical and histological results are discussed.

96. Gram-negative sepsis with acute renal failure. Occurrence from acute glomerulonephritis. A. R. Zappacosta and B. L. Ashby. J. Am. Med. Assoc. 238: 1389-1390, 1977.

Acute tubular necrosis is the term generally applied to the acute intrinsic renal failure that occurs after nephrotoxins, after surgery, during volume contraction or hypotension, or during gram-negative sepsis. A clinical syndrome of acute intrinsic renal failure occurring in these settings has become well known.

Acute intrinsic renal failure occurred in an adult patient with *Escherichia coli* septicemia. The clinical course did not include any of the circumstances usually present when acute renal failure complicates gram-negative sepsis. A renal biopsy showed acute proliferative glomerulonephritis. There was no evidence to support other known causes of acute parenchymal renal failure, such as poststreptococcal glomerulonephritis, subacute bacterial endocarditis, or vasculitis. The patient recovered completely with antibiotic therapy, and renal function returned to normal within two weeks. An immunologic mechanism involving *E. coli* was considered responsible for the acute renal failure.

97. Glucose oxidation during prolonged exercise evaluated with naturally labeled  $[^{13}\text{C}]$ glucose. F. Pirnay, M. Lacroix, F. Mosora, A. Luyckx, and P. Lefebvre. J. Appl. Physiol. 43: 258-261, 1977.

By use of naturally enriched  $[^{13}\text{C}]$ glucose as metabolic tracer, the utilization of exogenous glucose ingested during muscular exercise was investigated. Four subjects walked on an uphill treadmill for 2 hr, and three others for 4 hr. The energy expenditure, close to 50% of the individual maximum  $\dot{V}\text{O}_2$ , varied from 1.9 to 2.1 liters of  $\text{O}_2/\text{min}$  while the heart rate ranged between 142 and 165 beats/min. The subjects, who were on a mixed diet and had fasted overnight, were given 100 g of naturally labeled  $[^{13}\text{C}]$ glucose. Following this intake, the expired  $\text{CO}_2$  became rapidly enriched in carbon-13. The increase was observed as early as 15 min after the oral intake, and reached a maximum within 1-2 hr, when utilization of exogenous glucose varied between 500 and 650 mg/min, representing as much as 55% of the carbohydrate metabolism and 24% of the total energy expenditure. It should be pointed out that the energy supply afforded by exogenous glucose started to decrease 90 min after its ingestion. It seems therefore advisable to repeat glucose intake every 60-90 min for permitting lung-duration muscular exercise.

98. The effects of corticosteroids on mobilization and function of neutrophils. J. M. Mishler. Exper. Hemat. 5 (Suppl.): 15-32, 1977.

An analysis of the published data is complicated for the following reasons: a variety of different corticosteroid agents has been used, they have been administered by varying routes, and the tests of neutrophil function have differed greatly. Moreover results obtained in different animal species may or may not be directly comparable or relevant to man.

In trying to decide whether or not corticosteroids compromise neutrophil function, the author has tried to present the available information in a manner that permits a reasonable explanation for the results in the literature. A variety of pharmacological agents can be used to induce a neutrophil leucocytosis in man and so to increase the efficiency of granulocyte collection from donors undergoing leucapheresis. The contribution to

the neutrophilia induced by corticosteroids made by prolonged intravascular survival of neutrophils consequent on their impaired mobilization to extravascular sites may in the past have been overemphasized. The effects of corticosteroids on neutrophil function have been studied extensively. Conflicting results have been obtained. In general the data do not permit a conclusion that corticosteroids consistently compromise neutrophil function either *in vitro* or *in vivo*. For the present we may assume that the administration of corticosteroids to the donor is a satisfactory method of enhancing the efficiency of collection during leucapheresis and does not jeopardize the clinical efficiency of the collected cells.

99. Clinical aspects of body temperature regulation. F. T. Caldwell, Jr. Manual of Surgical Practice, 1975, W. B. Saunders, New York, pp. 115-128.

Regulation of body temperature by normal man:

a) Insensible evaporation. This process accounts for 25% of heat loss; one-half occurs through the skin and one-half by way of the respiratory tract.

b) Hypothermia associated with sepsis. Hypothermia occurring with overwhelming sepsis is a well known clinical syndrome. This paradoxical situation is usually accompanied by simultaneous failure of other organ systems involved in regulatory functions such as the lungs, heart and kidneys. Thus hypothermia under these conditions reflects impending total collapse of the host and has ominous prognostic significance. The mechanism of hypothermia with sepsis--central vs. peripheral failure--is poorly understood, but likely will be shown to include elements of both. Sepsis interferes with peripheral oxidative metabolism, and bacterial endotoxin may very well act directly on the hypothalamus.

c) Hyperthermia. The surgeon is required to care for patients with sustained hyperthermia of many etiologies. One should keep in mind the metabolic costs of elevation of the average body temperature. In man the major effect of fever is the result of the  $Q_{10}$  effect on rates of body reactions. Man's  $Q_{10}$  is between 2.3 and 2.9; thus, sustained elevation of the mean body temperature of  $1^{\circ}\text{C}$  would produce a 12.5 to 13% increase in the OCR and rate of heart production. The long-term demands of this increased heat production may be a deciding factor in the outcome in a depleted patient with a major metabolic challenge such as thermal injury or massive tissue necrosis with sepsis.

100. Substrate utilization during prolonged exercise preceded by ingestion of glucose. G. Ahlborg and P. Felig. Am. J. Physiol. 233: E188-E194, 1977.

Hypoglycemia has been described in connection with severe prolonged exercise. During submaximal prolonged exercise, a mild decrease in arterial glucose has been shown to be due to the failure of splanchnic glucose output to keep pace with the increased glucose consumption by exercising muscle. Administration of glucose during exercise is followed by a rising arterial glucose concentration, increased utilization of carbohydrate, and improved physical work capacity. Only limited observations are available on the effects of glucose ingestion prior to exercise.

The effect of ingestion of 200 g of glucose 50 min prior to initiation of 4 hr of exercise at 30% of maximal oxygen uptake was examined in healthy subjects. Glucose uptake by the exercising legs was 40-100% higher in the glucose-fed subjects, a result that accounted for 48-53% of leg oxygen consumption as compared to 27-41% in controls. It is concluded that glucose ingestion prior to exercise results in: a) augmented glucose uptake by the exercising leg; b) a diminution in lipolysis; c) increased splanchnic glucose escape in association with decreased hepatic gluconeogenesis. These responses may be mediated in part by the hyperinsulinemia and relative hypoglycagonemia induced by glucose feeding.

101. Stimulation of insulin and glucagon secretion by vasoactive intestinal peptide. M. Schebalin, S. I. Said, and G. M. Makhlof. Am. J. Physiol. 232: E197-E200, 1977.

In vivo, vasoactive intestinal peptide (VIP) produces simultaneous increases in blood glucose and insulin levels. In order to determine whether VIP, like its homologues, also stimulates insulin secretion directly, studies were made in controlled glucose media employing the vascularly perfused cat pancreas. VIP stimulated insulin secretion significantly in the presence of constant physiological concentrations of glucose. The highest insulin response to VIP approached the highest insulin response to glucose. In the absence of glucose, the insulin response to VIP was insignificant. Unexpectedly, VIP was found to be a more effective stimulant of glucagon than of insulin secretion. The highest glucagon response to VIP was attained in the presence of physiological concentrations of glucose and equalled the glucagon response obtained upon withdrawal of glucose from the perfusate. The glucagon response to VIP was blocked by increasing the glucose in the perfusate. These studies indicate that VIP present in pancreatic islets might play a role in the local control of pancreatic endocrine function.

102. Comparison of endotoxin detoxification by leukocytes and macrophages. J. P. Filkins. Proc. Soc. Exptl. Biol. Med. 136: 1396-1400, 1971.

Endotoxin detoxification by leukocyte and macrophage sonicates was evaluated using the lead-sensitized rat shock bioassay. Leukocyte sonicates from both blood and peritoneal exudates did not inactivate endotoxin. In contrast, sonicates of macrophages from liver, lung, or peritoneal exudates displayed marked endotoxin detoxifying ability. During the development of peritoneal exudates to casein ip, the cell progression from a neutrophilia to a macrophage population was associated with the development of exudate endotoxin detoxifying ability. Endotoxin inactivation was demonstrated in the large granule fraction of peritoneal macrophages. The probable specificity of macrophage lysosomes in certain aspects of endotoxin detoxification is discussed.

103. Management of patients in shock. T. Sugimoto, S. Shimazaki, H. Fusamoto, and Y. Onji. Jap. Circ. J. 41: 389-393, 1977.

Clinical study was conducted in the course of treatment of patients with hypovolemic and septic shock at Department of Traumatology, Osaka University Hospital. The authors have found large difference between data obtained in their study and experimental results obtained in animals. In hypovolemic shock of man, "taking up phenomenon" to abdominal organs was not observed. Therefore, if the shock does not respond to transfusion and infusion, other causes must be looked for. In patients whose shock state persisted more than 10 hours, death related to shock organs increased remarkably. The nature of septic shock in man is hyperdynamic state. Hemodynamic change

during the development of septic shock from sepsis was described and the difference from experimental research on endotoxin shock in animals was discussed.

104. Shock in patients with disseminated intravascular coagulation (DIC).  
T. Matsuda and K. Shimada. Jap. Circ. J. 41: 376-382, 1977.

Relationship between shock and disseminated intravascular coagulation (DIC) was investigated in 699 consecutive autopsied cases. The diagnosis of DIC was made when consumption coagulopathy was observed. Among these patients, 106 cases had evidences of DIC and 30 ones had clinical and pathological findings highly suggestive of DIC although the coagulation findings were nonspecific. Shock was complicated in 38 of the former and in 10 of the latter. In 32 of these 48 cases with shock, coagulation abnormalities were observed simultaneously with or after the development of shock. The most common underlying disease in these patients was gram-negative septicemia, gastrointestinal hemorrhage and myocardial infarction caused DIC less frequently. In the other 16 cases, about 70% of which was patients with metastatic cancer of the gastrointestinal or biliary tracts, shock developed after the diagnosis of DIC was established, although marked exaggeration of the coagulation findings was observed following shock. Levels of factor XII and C3 in plasma decreased in DIC. Especially, depletion of factor XII was remarkable in cases with septic shock. The most important clinical symptom in patients with DIC associated with shock was acute renal failure. Administration of low doses of heparin to DIC improved coagulation abnormalities frequently, however no beneficial effects on symptoms other than bleeding, i.e. acute renal failure, were observed. Examination of autopsy material showed that fibrin thrombi were present in about 70% of these cases. It is concluded that shock is frequently accompanied with DIC and the patients with shock should be treated with heparin as soon as possible whenever DIC was suspected.

105. Pathophysiology of shock. K. Okada, I. Kosugi, T. Kitagaki, Y. Yamaguchi, H. Yoshikawa, J. Kawashima, S. Kawakami, and Y. Senoh. Jap. Circ. J. 41: 346-361, 1977.

Pathophysiology of shock was fundamentally investigated in several different ways:

- a) Fractional distribution of cardiac output was measured, using radioactive microsphere technique. Hemorrhagic, endotoxin and trimethaphan hypotension were compared to each other in their fractional distribution of cardiac output. As a whole, cardiac output was distributed in the way to maintain cerebral or coronary blood flow, whatever the cause of shock may be. This "centralization" was rather well maintained even shock progressed. Splanchnic blood flow, especially the pancreas flow, was decreased significantly. This may be related to the production of vasoactive or toxic substances from these organs.
- b) Myocardial depressant factor was identified both in plasma and pancreas in advanced shock. Gel-chromatographic analysis was applied to separate the myocardial depressant factor. It is also demonstrated that myocardial depressant factor was produced in pancreas, transported via blood stream to the heart and caused cardiac depression.
- c) In vivo cardiac contractility was measured by the change of Vmax sequentially as shock advanced. Left ventricular pressure was measured, using

catheter tip transducer. In hemorrhagic shock, cardiac contractility began to decrease 4 hrs after bleeding and continued to deteriorate progressively thereafter.

d) Regional coronary blood flow distribution was also measured by radioactive microsphere method. 2 hrs after bleeding, endocardial fractional distribution already began to decrease and remained in the same distributional pattern even 4 hrs after bleeding, while the myocardial contractility did not show any deterioration in 2 hrs after bleeding. So it may be said that endocardial ischemia had no significant relationship with this cardiac dysfunction.

f) Phagocytic function was decreased progressively when shock advanced. Reticuloendothelial depressing substance was also analyzed using gel-chromatographic method. Bioassay of RDS was shown by the decrease of phagocytic index after administering this fraction to healthy rats.

g) Closed loop, negative feedback mechanism was suggested with relation to the above mentioned results. Decrease of cardiac output, followed by decrease of splanchnic blood flow, might cause the production of myocardial depressant factor. And this MDF might exert again decrease of cardiac contractility, thus closed negative feedback loop was established. This mechanism might be called as "peripheral theory" for cardiac deterioration in shock. MDF, lysozymal enzymes or other vasoactive substances could not be phagocytized because of the reticuloendothelial system dysfunction, which may be caused by the decrease in opsonin activity or the release of reticuloendothelial depressing substance.

106. Autoglycolysis in leukemic and nonleukemic blood. H. M. Rawnsley and H. M. Bowman. Am. J. Med. Sci. 249: 203-210, 1968.

Artifactual or factitious hypoglycemia from the in vitro utilization of glucose has been reported in patients with leukemia. From earlier investigations it was known that on standing there would be a decrease in the glucose concentration in whole normal blood and an even greater decrease in the blood from patients with leukemia. In whole blood the white cells, when present in increased numbers, apparently can contribute significantly to the utilization of glucose. The initial glucose concentration within a limited range does not affect the degree or rate of glycolysis. Plasma factors do not appear to be important in the rate of glucose utilization.

In vitro utilization of glucose in leukemic blood may result in an artifactual or factitious hypoglycemia. By removing the buffy coat it can be shown that the white blood cells contribute significantly to the autoglycolysis. Glucose determinations were done at hourly intervals. The glucose consumption in the nonleukemic bloods was 5-7 times greater than in the leukemic bloods with comparable white blood cell counts. Not until the WBC count was over 60,000/c.mm. did the leukemic bloods utilized more glucose than the controls.

107. Systemic vascular performance in endotoxic shock. A. E. Seyfer, R. Zajtchuk, D. R. Hazlett, and L. A. Mologne. Surg. Gynec. Obstet. 145: 401-407, 1977.

Over 150 years ago, Laennec first recognized the occurrence of a shocklike state associated with infection. Since that time, due to the high mortality associated with this syndrome, there has been increasing interest in septic shock in both surgical and nonsurgical patients. Lefer and Clowes and

colleagues stated that the responsible factors in the development of cardiovascular decompensation include hypovolemia secondary to fluid translocation, increased pulmonary vascular resistance accompanied by right ventricular failure and myocardial depression. Pulmonary changes in this setting, including capillary congestion and interstitial edema, accompany increased pulmonary vascular resistance. A circulatory factor with a direct, depressive action on the myocardium has been postulated, although its existence has been disputed by Hinshaw and colleagues, and the mechanism of myocardial depression remains obscure. The decreased venous return seen in all species may occur as a result of sequestration of blood upstream from constricted veins. Increases in capillary hydrostatic pressure due to venous constriction, decreases in colloid osmotic pressures and changes in capillary permeability may effectively combine to produce an extravascular accumulation of fluid. Endotoxin may directly affect vascular smooth muscle to change resistance significantly, initiating the entire spectrum. The precise chain of events leading to this change in resistance was the subject of this investigation.

Sixteen dogs were studied in an effort to investigate certain peripheral vascular and metabolic parameters in endotoxic shock. Cardiopulmonary bypass was instituted for 12 of the dogs to study systemic parameters at constant circulatory flow rates. From these studies, it appears that endotoxin is capable of initiating profound hemodynamic and metabolic changes. Initially, cardiac output and arterial pressure drop precipitously, despite a transient rise in systemic and pulmonary vascular resistance. Subsequently, peripheral arterial pressures and systemic vascular resistance continue to decline, even if arterial flow remains at constant levels. Oxygen extraction by peripheral tissues decreases after endotoxin injection, despite adequate oxygen availability and constant hemoglobin levels.

108. Bacterial shock. H. Shubin, M. H. Weil, and R. W. Carlson. Am. Heart J. 94: 112-114, 1977.

The majority of cases of bacterial shock are caused by gram-negative enteric bacilli. Bacteremia is rarely complicated by shock in persons under the age of 40, except in women during pregnancy and in neonates. If patients with septic abortion are excluded, bacterial shock is more frequent in men than in women, reflecting the higher incidence of urinary tract infections in older men. Diabetes, chronic liver disease, and blood dyscrasias predispose to bacteremia and shock. Bacteremia with shock is usually precipitated by a manipulative procedure.

Bacterial shock due to gram-negative bacilli is best managed by prompt control of the infection with appropriate antibiotics and surgical drainage or excision. Corticosteroids for purposes of controlling systemic reactions to bacteria and their toxins constitute adjunctive therapy. Volume repletion and respiratory support may be of the greatest importance for temporary support of these critically ill patients. Vasoactive drugs including dopamine and isoproterenol should be used very sparingly and only as very temporary expedients.

109. Carotid artery loop for repeated catheterization of the left ventricle in dogs. M. A. Meier and D. M. Long, Jr. Surgery 70: 797-799, 1971.

A technique for surgical preparation of carotid artery is described. The carotid artery is dissected and enveloped in a skin flap creating a loop. After the healing, the preparation can be used for repeated catheterization

of the left ventricle and arterial blood sampling in unanesthetized dogs. With two tapes to control and prevent hematomas, the artery is punctured and the catheter introduced. With no permanent catheters through the skin, the method has been used for over 12 months without failure.

110. Effect of angiotensin-converting enzyme inhibitor (SQ 20881) on the plasma concentration of angiotensin I, angiotensin II, and arginine vasopressin in the dog during hemorrhagic shock. J. J. Morton, P. F. Semple, I. McA. Ledingham, B. Stuart, M. A. Tehrani, A. R. Garcia, and G. McGarrity. Circ. Res. 41: 301-308, 1977.

The effect of an angiotensin-converting enzyme inhibitor on the circulating levels of angiotensin I, angiotensin II, and arginine vasopressin was studied in dogs subjected to hypotensive hemorrhagic shock. In dogs subjected to hemorrhage but not given the inhibitor, angiotensin II rose 20-fold whereas in dogs subjected to hemorrhage but pretreated with the inhibitor, angiotensin II rose only 2-fold. In the pretreated dogs angiotensin I rose 30-fold. There was no statistically significant difference between the vasopressin levels found in the untreated dogs and the levels found in dogs given the inhibitor. Of the 15 dogs in the untreated group, 5 died before retransfusion was completed (4 of cardiac failure and 1 of cardiac arrhythmia); none of the 10 dogs in the inhibitor-treated group died. These observations suggest that the very high levels of angiotensin II observed following severe hemorrhage do not contribute significantly to the increased secretion of vasopressin and that the inhibitor protects against death, possibly by suppressing the very high blood levels of angiotensin II observed following this type of experimental hemorrhagic shock.

111. Feline endotoxin shock: Effects of methylprednisolone on kininogen-depletion, on the pulmonary circulation and on survival. N. Al-Kaisi, J. R. Parratt, H. H. Siddiqui, and I. J. Zeitlin. Br. J. Pharmac. 60: 471-476, 1977.

Escherichia coli endotoxin, administered i.v. in a dose of 2 mg/kg to pentobarbitone-anesthetized, artificially ventilated cats resulted in pulmonary hypertension, systemic hypotension and an immediate 30-40% reduction in plasma kininogen, an effect which probably indicates a release of plasma kinins. Methylprednisolone (30 mg/kg), when administered 30 min before endotoxin, did not influence the endotoxin-induced pulmonary hypertension or systemic hypotension but completely prevented the depletion of plasma kininogen. In spontaneously breathing cats, methylprednisolone, administered 30 min after endotoxin, caused a rapid repletion of kininogen and prolonged survival (47% at 6 hr compared to 10% in the endotoxin-alone animals). Methylprednisolone did not appear to influence lactate production or the hyperventilation observed during the delayed endotoxin shock phase. It is concluded that methylprednisolone does not prevent the release, by endotoxin, of a pulmonary vasoconstrictor prostaglandin, or its effects, but that perhaps by preventing kinin release it may reduce endotoxin-induced capillary leakage.

112. The effect of leukocyte and platelet transfusion on the activation of intravascular coagulation by endotoxin in granulocytopenic and thrombocytopenic rabbits. E. Bohn and G. Muller-Berghaus. Am. J. Path. 84: 239-258, 1976.

The effect of transfusion of peritoneal leukocytes, platelets, or cell suspension medium on the activation of intravascular coagulation and on the

generation of capillary microclots was studied in 51 granulocytopenic and thrombocytopenic rabbits. Granulocytopenia and thrombocytopenia induced by feeding the cytotoxic drug busulfan prevented the activation of intravascular coagulation and the occurrence of renal glomerular microclots after two injections of endotoxin. The transfusion of platelets into busulfan-pretreated rabbits increased the mean platelet count from 2400 to 205,000 cells/ $\mu$ l, but platelet-transfused rabbits did not exhibit activation of intravascular coagulation after endotoxin injection. If, however, granulocytopenic and thrombocytopenic rabbits were transfused with peritoneal leukocytes before the second injection of endotoxin, activation of intravascular coagulation occurred, and microclot formation in renal glomerular capillaries was observed in a high percentage of animals. Positive reactions to endotoxin were obtained in leukocyte-transfused rabbits even with platelet counts of 1000 cells/ $\mu$ l before the second injection of endotoxin. Thus platelets do not seem to be essentially involved in the activation of intravascular coagulation by endotoxin, whereas the presence of leukocytes is required for triggering endotoxin-induced generalized intravascular coagulation.

113. Activation of intravascular coagulation by endotoxin: the significance of granulocytes and platelets. G. Muller-Berghaus, E. Bohn and W. Hobel. Br. J. Haematol. 33: 213-220, 1976.

The importance of granulocytes and/or platelets in endotoxin-induced generalized intravascular coagulation was studied in neutropenic as well as thrombocytopenic rabbits. Neutropenia and thrombocytopenia were induced by oral administration of busulphan. Generalized intravascular coagulation, as indicated by renal glomerular microclot formation, was initiated by two intravenous injections of endotoxin. Granulocyte counts before the second injection of endotoxin were most significantly related to activation of intravascular coagulation whereas platelet counts either before the first or second injection of endotoxin were not definitely related to the activation process. Renal glomerular microclots occurred in rabbits after two injections of endotoxin even when the platelet counts were between 500 and 5000/ $\mu$ l. These experiments indicated that granulocytes but not platelets are essential to the activation of endotoxin-induced intravascular coagulation.

114. Disseminated intravascular coagulation induced by endotoxin: rabbit model and man. J. Hawiger. Animal Models of Thrombosis and Hemorrhagic Diseases, DHEW Publication No. (NIH) 76-982, 1975, pp. 49-54.

Bloodstream infections due to endotoxin-producing gram-negative bacteria prevail as a cause of disseminated intravascular coagulation (DIC) in man. Patients suffering bacteremia due to endotoxin-producing gram-negative rods represent the highest-risk group for development of DIC. Approximately 71,000 patients per year in the United States develop gram-negative bacteremia; it is estimated that 18,000 deaths result. DIC and shock complicating these bacteremic episodes contribute substantially to mortality in this large population of patients. Many of the patients undergo a variety of procedures (surgery, immunosuppression for organ transplants, and cancer chemotherapy), and infections associated with DIC become serious and costly consequences of medical progress. The need for a model of gram-negative bacterial infection that uniformly results in DIC is apparent.

Injection of endotoxin into rabbit and man evokes a fever. This pyrogenic response serves as an index of the biologic activity of endotoxins. In this respect, the rabbit is approximately 10 times more resistant to endotoxin than man. The response of the rabbit fibrinolytic system to a variety of known inducers of fibrinolysis is slow. In contrast the fibrinolytic response in man is prompt and reaches a high level of activity. This is illustrated by experiments on 67 volunteer patients. They revealed that i.v. injection of two different bacterial lipopolysaccharides (endotoxin) in doses of 0.2 and 300  $\mu$ g respectively, caused striking activation of fibrinolysis within 2 hrs following a single endotoxin injection. Activation of fibrinolysis could not be induced experimentally with the same preparation of endotoxin in rabbits. This suggests that reactivity of the fibrinolytic system to endotoxin differs in man and this experimental animal.

These examples of differences in the selected elements of blood clotting and fibrinolytic systems of the rabbit and man may shed light on the well-known fact that with endotoxin it is extremely difficult to elicit changes suggesting intravascular coagulation in the blood of normal healthy people. In contrast, similar injections into rabbits or guinea pigs induce such changes. This paradox calls for caution in applying the results of endotoxin-induced DIC in rabbits to the clinical situation in man. The efforts to find new models of DIC induced by endotoxin, resembling more closely human response, should take into consideration those characteristics of blood clotting and fibrinolytic systems that are responsible for sensitivity or resistance to endotoxin. The dynamics of response to endotoxin in elements of blood clotting and fibrinolytic systems may produce an entirely different pattern of changes in different species.

115. Heparin therapy in septicemia with disseminated intravascular coagulation. Effect on mortality and on correction of hemostatic defects. J. J. Corrigan, Jr., and C. M. Jordan. New Engl. J. Med. 283: 778-782, 1977.

Of 26 children with septic shock studied for coagulation defects, 24 received heparin in addition to standard therapy. Disseminated intravascular coagulation was diagnosed in 96%. Of the heparin-treated patients 58% died in shock; laboratory evidence of improvement in the coagulation defects occurred in all who survived and three who died in shock. The presence of hypofibrinogenemia indicated a very poor prognosis but did not necessarily mean that shock was irreversible. Thus, heparin does not appear to improve survival in patients with septicemia and associated hypotension but may improve the coagulation defects. Improvement in the hypotension probably has a major role in abolishing disseminated intravascular coagulation.

116. Low-dose intravenous heparin in the treatment of disseminated intravascular coagulation. V. Gurewich and G. Lipinski. Am. J. Med. Sci. 274: 83-86, 1977.

A critically ill patient with disseminated intravascular coagulation (DIC) secondary to gram negative septicemia is reported. Low dose (5-10  $\mu$ g/h) heparin by intravenous infusion promptly inhibited intravascular coagulation, as reflected by laboratory studies. Fibrin monomer (FM) became undetectable, concentration of fibrin degradation products (FDP) fell, fibrinogen rose, and the activated partial thromboplastin time (PTT) shortened. Unintentional, temporary interruption of heparin resulted in transient return of abnormal laboratory values. The patient went on to make a complete recovery. Although the therapeutic contribution of heparin could not be proven in

this patient, the laboratory data suggested that it was a valuable adjunct and in the dosage given unlikely to potentiate bleeding. The monitoring of heparin therapy in DIC by measurement of FDP, FM, and fibrinogen rather than clotting time is recommended.

117. Gravity leucapheresis--a new method for collection of transfusible granulocytes. I. Djerassi. Exp. Hemat. 5 (Suppl.):139-143, 1977.

Transfusions of granulocytes (PMNs) collected from normal donors by filtration leucapheresis (FL) or by leucapheresis with continuous flow centrifugation (CFC) can help to control infections in leucopenic patients. A simple method for leucapheresis is described that differs from other leucapheresis techniques used previously. Existing methods are based on the use of centrifugal force or selective filtration to separate and harvest WBCs. This new method uses gravity unassisted by centrifugation. The acceleration of the separation of PMNs by a macromolecular colloid (HES) in low viscosity saline makes this method practical for pheresis of large blood volumes. The efficiency of PMN recovery by this method is over 80% as compared to 20% for HES-assisted CFC. The advantages of gravity leucapheresis (GL) over separation by CFC or by FL can be summarized as follows: the yield of PMNs per unit time using GL is equal or superior to pheresis by CFC; the volume of blood processed by GL is 1/4 of the volume that must be processed to harvest the same number of cells by CFC pheresis; heparinization of the donor is not needed as it is in FL or some CFC procedures.

118. Granulocyte transfusion therapy--a review of the practical aspects of collection and transfusion techniques. R. G. Graw, Jr., and F. R. Appelbaum. Exp. Hemat. 5 (Suppl.): 39-48, 1977.

Granulocyte transfusion therapy has been widely accepted for the treatment of infections associated with granulocytopenia. Three techniques have been developed each of which is capable of safely collecting large numbers of PMNs from normal donors. Each method has its own particular advantages and limitations. Appropriate recipient selection has been difficult to define. Most investigators agree that life-threatening bacterial infections which fail to respond to initial antibiotic therapy should be treated with high dose, daily PMN transfusions. The toxicities of PMN transfusions for the recipient can range from none to a major cardiovascular collapse seen following infusion of grossly incompatible or contaminated buffy coat. When donors are selected for erythrocyte and WBC antigen compatibility, transfusion reactions, if they occur, are usually characterized by mild fever and chills which readily respond to antihistamines, antipyretics, and/or meperidine. The available techniques for collection and transfusion will require further refinement.

119. The effect of dextran 40 and blood transfusion on hepatic circulation and oxygen consumption in hemorrhagic shock. B. Lindberg and N. Darle. J. Surg. Res. 23: 264-273, 1977.

It was previously shown that dogs subjected to severe hemorrhagic shock survived if their livers were perfused with blood from a healthy donor dog during the shock period, but died if the perfusion was given into the jugular vein. For successful treatment of hemorrhagic shock the circulation and perfusion of the liver must be rapidly restored. Hemorrhagic shock is known to produce a cellular aggregation in the hepatic sinusoids, thereby blocking the microcirculation in the liver. A similar type of aggregation was caused by infusion of high molecular weight dextran and this aggregation was readily dissolved by infusion of low molecular weight dextran, thereby

enhancing the perfusion. The aim of this study was to compare the effect of treatment with dextran 40 and blood on the hepatic circulation and oxygen consumption in hemorrhagic shock.

After treatment with the shed blood the flow in the hepatic artery and portal vein returned to preshock values and the oxygen consumption was 39% higher than the initial values. After treatment with dextran 40 the flow in the hepatic artery was 91% higher than the initial value and the flow in the portal vein was 127% higher. In spite of these high flow values, the oxygen consumption was significantly lower in the dextran 40 group. In the second period of shock flow values were reduced to approximately the same values as in the first period but the oxygen consumption was significantly lower in the dextran 40 group than in the blood transfusion group.

120. Hepatic reticuloendothelial protection against bacteremia in experimental hemorrhagic shock. B. J. Pardy, R. C. Spencer, and H. A. F. Dudley. Surgery 81: 193-197, 1977.

Gram-negative septicemia is an increasingly common problem, and various suggestions have been made about the cause. One not often considered is that it may be the result of failure of hepatic removal of organisms which have crossed the intestinal mucosal barrier from the large bowel lumen to the portal blood stream. Splanchnic hypoperfusion both increases mucosal permeability and reduces the ability of the hepatic reticuloendothelial system (RES) to remove particulate matter from the blood. If RES function is reduced further by blockade with colloidal carbon, then any tendency for bacteremia to occur in shock might be enhanced. Splenectomized greyhounds, who had received a portal perfusion of either colloidal carbon or saline, were subjected to a period of hypovolemia and then were resuscitated. Peripheral blood cultures were sterile at all times in the control animals and before bleeding in the dogs that received carbon. However, all the RE-blockaded animals developed bacteremia during shock. It was concluded that hepatic RES function was essential in the prevention of bacteremia in the hypovolemic dog and that investigation should be directed toward studies of RES function in man with a view to determining the importance or otherwise of the RES in relation to gram-negative bacteremia.

121. Intercellular junctions in "shock lung": a freeze-fracture study. R. Barrios, S. Inoue, and J. C. Hogg. Lab. Invest. 36: 628-635, 1977.

Intercellular junctions in the alveolar epithelium and in the capillary endothelium in lung from five dogs after hemorrhagic shock (mean blood pressure, 40 mmHg for 3 hrs) and from 5 control dogs were observed in the electron microscope using the freeze-fracture technique. Following shock zonulae occludentes (tight junctions) in the alveolar epithelium showed alterations in substructure that were not present in control animals. These changes were morphologically similar to those reported in junctions altered after exposure to osmotic gradients with marked degradation and disappearance of junctional organized "leaky" type in control animals, was generally unaltered after shock. Disintegration and disappearance of junctional strands in "focal" regions, however, were occasionally observed. The increased pulmonary capillary permeability observed physiologically after hemorrhagic shock could be explained by such alterations of endothelial zonulae occludentes.

122. Blood flow in hepatic sinusoids in experimental hemorrhagic shock in the rat. A. Koo and I. Y. S. Liang. Microvasc. Res. 13: 315-325, 1977.

Sequential changes of blood flow in the hepatic sinusoids were measured in anesthetized rats which were subjected to the Wiggers method of hemorrhagic shock. The ventral margin of the liver was transilluminated by a fiber-optic light-guide and observed microscopically by a televison method. Systemic arterial and portal venous pressures and several direct quantitative microvascular measurements in the sinusoids were recorded, including diameter, erythrocyte velocity, and erythrocyte flux, from which blood flow, hematocrit index, and flow resistance were indirectly calculated. In the initial phase of hemorrhage, hepatic sinusoids constricted with reduced blood flow but showed increased flow resistance and progressive hemoconcentration. When hemorrhage was severe, flow in about two-thirds of the sinusoids observed became stagnant; some of them also dilated while others remained constricted. The possible mechanism for these responses in the hepatic sinusoids to hemorrhagic shock is also discussed.

123. Summary of Poster Session I, ISOTT Symposium. Current problems in tissue oxygenation. J. Strauss and L. Mela. Microvasc. Res. 13: 421-424, 1977.

Five major areas were presented and discussed in the poster session of the International Society on Oxygen Transport to Tissue, Anaheim Symposium: efficiency of hemoglobin and other O<sub>2</sub>-carrying systems, organ blood flow and its regulation, techniques for determination of tissue oxygenation, enzyme adaptation in systemic hypoxia, and prevention or decrease of the detrimental tissue effects of ischemia.

124. Effects of an intravenous amino acid nutrient solution on left ventricular contractility in dogs. R. M. Abel, V. A. Subramanian, and W. A. Gay, Jr. J. Surg. Res. 23: 201-206, 1977.

The effects of an intravenous infusion of mixed essential and non-essential amino acids on left ventricular performance in the canine isovolumetric left heart preparation are mildly positively inotropic and infusion also results in an increase in left ventricular diastolic compliance. The mechanism of these actions has not yet been elucidated, but may be related to utilization of glucogenic amino acids directly by the myocardium. It appears that the clinical use of these crystalline amino acid solutions is a safe method of delivering nitrogen substrate for the purposes of parenteral nutrition in patients with compromised cardiac function, since there appears to be no evidence of a detrimental cardiac effect.

125. A new limulus assay for the detection of endotoxin. N. S. Harris and R. Feinstein. J. Trauma 17: 714-718, 1977.

The limulus amebocyte lysate (LAL) assay has proven to be a highly sensitive and reliable indicator of endotoxin in most biological fluids; however, it has not been a reliable indicator when used with blood because of different inhibitors present in the blood. To avoid these problems, investigators have used difficult extraction procedures, but even with these, results were often-times not uniform. It was found that a recently developed inert polymer (PSI-HAP 100) has a specific affinity for endotoxin, so that it was possible to develop a simple, reliable, reproducible method for the detection of endotoxin in blood. In the assay procedure, the polymer, compressed into a 3-mm diameter bead, is incubated with 0.2 cc of heparinized whole blood.

The bead is then removed from the blood, washed in pyrogen-free saline to remove any inhibitors of the LAL, and placed in a tube containing LAL. The LAL and bead are incubated together; after incubation the LAL is examined for gellation. Using this new method, it was possible to predict gram-negative septic episodes in burn patients several days before sepsis evolved clinically.

126. Effect of burn trauma on glucose turnover, oxidation, and recycling in guinea pigs. R. R. Wolfe and J. F. Burke. Am. J. Physiol. 233: E80-E85, 1977.

The simultaneous primed-constant infusion of [ $6-^3\text{H}$ ]- and [ $\text{U}-^1\text{C}$ ]glucose was used to determine the effect of burn injury on glucose turnover, oxidation, and recycling in guinea pigs. Eleven burned animals survived more than 72 hr (survivors), whereas five died between 60 and 72 hr postburn. All of the control (n=9) survived more than 72 hr. At 48 hr postburn, glucose turnover in the burned survivors was elevated 40% above that in control animals. A greater portion of the burned survivors' turnover was due to recycling and less was directed towards oxidation. The nonsurvivors had both a significantly depressed rate of appearance of glucose and an increased glucose clearance rate. Consequently, they were profoundly hypoglycemia and had a low rate of glucose oxidation. The alterations in glucose kinetics and oxidation apparent after burn did not reflect an inability of burned animals to oxidize exogenously infused glucose, however, because a 2-hr infusion of 55  $\mu\text{mol}/\text{kg}/\text{min}$  of unlabeled glucose doubled glucose oxidation in the burned survivors and tripled it in the nonsurvivors.

127. Limitations of the usefulness of the limulus assay for endotoxin. R. J. Stumacher, M. J. Kovnat and W. R. McCabe. New Engl. J. Med. 288: 1261-1264, 1973.

Gelation of lysates of amebocytes of the horseshoe crab has been proposed as a highly sensitive and specific bioassay for endotoxin that might be of diagnostic value in infections due to gram-negative bacteria. To assess the diagnostic value of the test and evaluate the role of endotoxin in such infections, limulus assays were performed on 694 specimens collected during 344 episodes of suspected bacteremia and compared with qualitative and quantitative blood cultures. Positive assays were obtained from 28 of 65 patients (43%) with bacteremia due to gram-negative bacilli and in 11 of 43 patients (26%) with localized infections due to gram-negative organisms. However, the occurrence of positive assays in 8 of 22 patients (36%) with infections due to gram-positive bacteria, who had no concomitant infections with gram-negative organisms, casts doubt on the diagnostic value of the new assay. In addition, no correlation was found between positive assays and the number of circulating gram-negative bacilli or the occurrence of shock or death.

128. Evidence for enhanced uptake of ATP by liver and kidney in hemorrhagic shock. I. H. Chaudry, M. M. Sayeed, and A. E. Baue. Am. J. Physiol. 233: R83-R88, 1977.

It has been shown that infusion of ATP- $\text{MgCl}_2$  proved beneficial in the treatment of shock; however, it is not known whether this effect is due to improvement in the microcirculation or direct provision of energy or a combination of the above or other effects. To elucidate the mechanism of the salutary effect of ATP- $\text{MgCl}_2$ , we have now examined the *in vitro* uptake of ATP by liver and kidney of animals in shock. Rats were bled to a mean arterial pressure of 40 Torr and so maintained for 2 hr. After the rats were killed, liver and kidney were removed and slices of tissue were incubated for 1 hr in 1.0 ml of

Krebs-HCO<sub>3</sub> buffer containing 10 mM glucose, 5 mM MgCl<sub>2</sub>, and 5 mM [8-<sup>14</sup>C]ATP or 5 mM [8-<sup>14</sup>C]ADP, or 5 mM [8-<sup>14</sup>C]AMP, or 5 mM (8-<sup>14</sup>C]adenosine in 95% O<sub>2</sub>-5% CO<sub>2</sub> and then homogenized. Tissue and medium samples were subjected to electrophoresis to separate and measure the various nucleotides. The uptake of [<sup>14</sup>C]ATP but not that of [<sup>14</sup>C]ADP or [<sup>14</sup>C]adenosine by liver and kidney slices from animals in shock was 2.5 times greater than the corresponding uptake by control slices. Thus, the beneficial effect of ATP-MgCl<sub>2</sub> in shock could be due to provision of energy directly to tissue in which ATP levels were lowered.

129. Acid-base relationships in the different body compartments: The basis for a simplified diagnostic approach. J. L. Gamble, Jr., and J. A. Bettice. Johns Hop. Med. J. 140: 213-221, 1977.

Special characteristics of cellular buffering must be taken into account in order to describe accurately acid-base relationships in the whole body. In particular, tissues other than blood are able to neutralize mineral acid independent of changes in pCO<sub>2</sub> and hence independent of large changes in extra- and intracellular pH. Although mechanistic details remain to be clarified, relationships that describe this tissue buffering in quantitative terms are well established. In this report, emphasis is placed on quantitative relationships that stress the need for diagnostic interpretation derived from acid-base changes within the whole body rather than simply within the blood compartment. Theoretical problems with respect to buffering mechanisms in various body compartments are reviewed and analyzed.

130. The role of adrenergic receptors and Ca<sup>2+</sup> in the action of endotoxin on human fat cells. I. Hikawyj-Yevich and J. A. Spitzer. J. Surg. Res. 23: 233-238, 1977.

Incubation of isolated human adipocytes with Escherichia coli endotoxin increases basal lipolysis without influencing basal cAMP levels. Hormonally stimulated fatty acid release (norepinephrine 1.2  $\mu$ M; isoproterenol, 0.95  $\mu$ M) is depressed by endotoxin, while norepinephrine-stimulated cAMP concentrations remain unchanged. The blocker, propranolol (10<sup>-2</sup> mM), depresses norepinephrine-stimulated lipolysis, and endotoxin does not alter its actions. Phentolamine (the  $\alpha$  blocker, 10<sup>-2</sup> mM) enhances norepinephrine-stimulated lipolysis and also cAMP levels. Endotoxin alters the cellular response to this blocker such that its stimulatory influence on norepinephrine-induced glycerol release and cAMP levels is depressed.

The divalent cation ionophore A23187 stimulates basal and norepinephrine-induced glycerol release with no influence on the release of fatty acids. These actions do not appear to be mediated via a cAMP mechanism since ionophore has no influence on basal and depresses norepinephrine-stimulated cAMP levels. Preincubation of cells with endotoxin does not alter A23187 action on glycerol release. However, endotoxin does obviate the depressant action of the ionophore on norepinephrine-stimulated cAMP concentrations.

The results indicate that under these experimental conditions endotoxin may be altering the activity of the  $\alpha$  receptor, while not interfering with the  $\beta$  receptor. Similarities between endotoxin and ionophore actions are compatible with the hypothesis that endotoxin may be exerting its influence on the cellular level, at least in part, by acting as an ionophore.

131. The effect of dextran 40 and blood transfusion on hepatic circulation and oxygen consumption in hemorrhagic shock. B. Lindberg and N. Darle. J. Surg. Res. 23: 264-273, 1977.

The flow in the hepatic artery and the portal vein, as well as the oxygen consumption of the liver, were studied in the pig in a standard shock model. The animals were bled to 50 mmHg arterial pressure and kept at this pressure for 30 min, one group being treated with the shed blood and the other group with an equal volume of dextran 40. Thirty minutes after completion of the treatment, the animals were once again bled to 50 mmHg and kept at this level for 30 min. During the first period of shock the flow in both vessels decreased to 53% of the baseline value and the oxygen consumption fell to 41% of the initial values.

After treatment with the shed blood the flow in the hepatic artery and portal vein returned to preshock values and the oxygen consumption was 39% higher than the initial values. After treatment with dextran 40 the flow in the hepatic artery was 91% higher than the initial value and the flow in the portal vein was 127% higher. In spite of these high flow values, the oxygen consumption was significantly lower in the dextran 40 group. In the second period of shock flow values were reduced to approximately the same values as in the first period but the oxygen consumption was significantly lower in the dextran 40 group than in the blood transfusion group.

132. Kinetics of phagocytosis and bacterial killing by human polymorphonuclear leukocytes and monocytes. P. K. Peterson, J. Verhoef, D. Schmeling, and P. G. Quie. J. Infect. Dis. 136: 502-509, 1977.

Two morphologically distinct phagocytic cell populations are found in human peripheral blood: polymorphonuclear leukocytes (PMNLs), composed primarily of neutrophilic granulocytes, and monocytes (MNs). Both are derived from precursor cells in the bone marrow, and PMNLs are released in a fully differentiated state; MNs, however, are capable of further differentiation into macrophages of the reticuloendothelial system. Clearly, both PMNLs and MNs play a fundamentally important role in host defense against bacterial infection. Patients with quantitative or qualitative defects of these phagocytic cells suffer recurrent and severe infections with a variety of microorganisms.

The kinetics of phagocytosis and bacterial killing by normal human PMNLs and by MNs were compared by use of (<sup>3</sup>H]thymidine-labeled *Staphylococcus aureus*, *Escherichia coli*, and *Listeria monocytogenes*. The rate of phagocytosis by PMNLs was approximately twice that by MNs for all three bacterial species. Although a marked difference was found in opsonic requirements for phagocytosis of *S. aureus*, *E. coli*, and *L. monocytogenes*, phagocytosis by PMNLs and MNs was mediated via the same serum factors. All three species were killed rapidly once they were associated with leukocytes; however, the rate of killing by MNs was slower than that of PMNLs. The slower rate of killing appeared to be secondary to slower ingestion of attached bacteria by MNs. Thus, PMNLs and MNs appear to possess receptors with specificity for the same bacterial opsonins; however, PMNLs are capable of more efficient bacterial phagocytosis (attachment and ingestion) than are MNs.

133. Clinical conditions associated with defective polymorphonuclear leukocyte chemotaxis. P. G. Quie and K. I. Cates. Am. J. Path. 88: 711-725, 1977.

Patients with granulocyte disorders have frequent infections, and the clinical manifestations are quite similar whether the disorder is insufficient numbers of cells or cell dysfunction. Infections tend to be prolonged, there is poor response to appropriate antibiotics, and recurrent infections are the rule. Rapid migration into tissues invaded by bacteria is a granulocyte function essential for host antibacterial defense. Patients with this granulocyte dysfunction may be infected by any of a wide spectrum of microorganisms.

Impressive numbers of clinical conditions are associated with defective leukocyte chemotaxis. In many, this cellular dysfunction is associated with other abnormalities of the immune response, but in others abnormal chemotactic responsiveness of leukocytes is the only abnormality of function identified in the laboratory. Patients are usually selected for study because of unusually severe, recurrent infections or poor response to antimicrobial agents, and therefore a frequent association between abnormality of chemotaxis and infection would be expected. Many patients demonstrate abnormal chemotaxis during remissions as well as during infections, and there seems little doubt that abnormality of chemotaxis is related to susceptibility to infections. Partial classification of disorders of chemotaxis was attempted. Major abnormalities are found when there is a primary cellular disorder or cell-directed inhibitors of chemotaxis are found. Less marked abnormalities are found when chemotactic factors are deficient.

134. The effect of hemorrhagic shock and resuscitation on regional blood flow in cynomolgus monkeys. M. J. Zinner, N. J. Gurll, and D. G. Reynolds. Circ. Shock 4: 291-296, 1977.

Recent attention has been directed at the species difference in response to various forms of experimental shock. Much of the work in primates has been done with rhesus monkeys (*Macaca mulatta*). However, the supply of rhesus monkeys available for biomedical research has recently been significantly reduced, and this limited availability will apparently worsen. The authors have evaluated the suitability of a related primate, the *Macaca fascicularis* (cynomolgus monkey), for use in shock research. In addition, since few studies have addressed the question of the hemodynamic response of primates to post-shock resuscitation, the following study investigates the effect of 4 hours of hemorrhagic hypotension and subsequent resuscitation with volume expansion and correction of acidosis on several regional circulations.

The effect of hemorrhagic hypotension and resuscitation on regional blood flow was studied in the *Macaca fascicularis* monkey. The majority of the splanchnic vasculature demonstrated a profound decrease in flow. Following fluid expansion and correction of acidosis, flow increased in these circulations but did not reach control values. Exceptions were the small bowel flow which fell only moderately and hepatic arterial flow which did not significantly change. Both coronary and adrenal circulations maintained flow during the shock and resuscitation periods, whereas brain and kidney blood flows fell significantly without recovery. There was a significant rise in serum glucose, lactate, and pyruvate during shock, with an increase in the lactate/!urivate ratio. Following resuscitation, the ratio decreased, implying a return toward aerobic metabolism.

135. Evidence for a centrally mediated hypotensive effect of *Escherichia coli* endotoxin in the anesthetized dog. D. E. Dobbins, D. L. Marciniak, E. F. Gersabeck, J. J. Maciejko, and G. J. Grega. J. Pharmacol. Exptl. Ther. 203: 47-55, 1977.

The centrally mediated cardiovascular effects of *Escherichia coli* endotoxin were studied utilizing a neurally intact, vascularly isolated head-trunk preparation in the anesthetized dog. The vascularly isolated head was perfused at constant flow with arterial blood supplied by a donor animal. Spectrophotometric examination of the donor and recipient trunk blood after administration of Evan's blue dye indicated that there was no blood exchanged between the head and trunk of the recipient dog. The responses to various physiological maneuvers and denervations indicated that the central nervous system and all afferents and efferents involved in the control of the cardiovascular system were functioning normally. The infusion of purified *E. coli* endotoxin into the arterial perfusion circuit to the head, either before or after bilateral denervation of the carotid sinus-body complexes, resulted in marked hypotension within 30 min in the trunk of the recipient dog. These findings indicate that purified *E. coli* endotoxin is capable of eliciting marked centrally mediated hypotensive responses. The time course of these responses suggests that the centrally mediated hypotensive effects of endotoxin do not participate in the initial precipitous fall in blood pressure seen after systemic administration of endotoxin, but rather that they may contribute significantly to the maintenance of the hypotension.

136. Control and complications of intermittent heparin therapy. C. S. Norman and J. L. Provan. Surg. Gynec. Obstet. 145: 338-342, 1977.

Heparin has a well recognized and vitally important role as a powerful anticoagulant in the prevention and treatment of thromboembolic states. Because it is only effective when given parenterally, administration is usually by continuous intravenous infusion or intermittent injection. There continues to be considerable division of opinion regarding the best mode of administration, the size of the dosage and how to control the dosage. A tendency to favor the continuous intravenous infusion of heparin for anticoagulation exists, and this form of therapy has been investigated in major studies.

A prospective study using an intermittent 6-hour method of heparin administration with control of subsequent dosage by the activated partial thromboplastin time revealed an over-all incidence of hemorrhagic complications of 12%. If surgical patients are excluded, the incidence of hemorrhage falls to 4%. This may be further reduced by monitoring the activated partial thromboplastin time within the therapeutic range. In no patient did thromboembolism recur while receiving heparin. It is suggested that this method provides adequate control of heparin therapy with an acceptable complication rate and adequate thromboembolic control and is cheaper to use than a continuous infusion.

137. Pulmonary insufficiency produced by norepinephrine: a comparison with epinephrine. J. L. Berk, J. F. Hagen, R. Tong, and G. Maly. Circ. Shock 4: 247-251, 1977.

For more than half a century the catecholamines have been known to be involved in the pathogenesis of shock. An infusion of epinephrine results in hypotension and death in animals, and the pathological findings are indistin-

guishable from those of animals dying from hemorrhagic or endotoxin shock. In shock of various causations, epinephrine and norepinephrine blood levels are significantly elevated and there is a negative correlation between the blood levels and survival. Conversely, animals made tolerant to epinephrine will survive otherwise lethal periods of endotoxin and hemorrhagic shock. There is abundant evidence that there is a causal relationship between prolonged increased catecholamine stimulation and the outcome of shock, and that the lung is a major target organ of this stimulation, which is frequently a cause of death. Thus knowledge of the pulmonary hemodynamic effects of epinephrine and norepinephrine is important for understanding the mechanisms involved in the pathogenesis of the pulmonary insufficiency of shock. Epinephrine, in amounts that can be produced endogenously in shock, has been shown to cause substantial pulmonary shunting. The purpose of this study is to determine the magnitude of the pulmonary insufficiency produced by norepinephrine and compare it with that produced by epinephrine.

An intravenous infusion of norepinephrine, 2  $\mu\text{g}/\text{kg}/\text{min}$ , for 5 hr in anesthetized, mechanically ventilated dogs produced a statistically significant increase in the pulmonary shunt, the cardiac output, and the mean pulmonary artery pressure, but no significant change in the pulmonary wedge pressure and the pulmonary vascular resistance except at 5 min. These hemodynamic changes are qualitatively similar to those produced by the same dose of epinephrine infused for the same time period. However, there were differences in the magnitude of the hemodynamic changes between norepinephrine and epinephrine, as might be expected on the basis of their different pulmonary pharmacologic effects, but the changes were not statistically significant at all times, and more studies are necessary to determine if the differences are real. These studies add support to the thesis that adrenergic stimulation plays an important role in the pathogenesis of the pulmonary insufficiency associated with shock.

138. Phagocytosis. Clinical disorders of recognition and ingestion. T. P. Stossel. Am. J. Path. 88: 741-751, 1977.

Tentative conclusions concerning the role of recognition and ingestion of microorganisms by phagocytes in host defense and the consequences of disorders of phagocytosis can be derived by correlating a) knowledge about recognition and ingestion derived from studies in vitro, b) investigations of the clearance of particulate matter from the circulation of animals and man, and c) analyses of the behavior of phagocytes in patients susceptible to recurrent pyogenic infections. Deficiency of the major serum recognition-conferring agents (immunoglobulins and complement proteins that deposit a fragment of C3 on microbes) prevents the optimal clearance of virulent encapsulated pathogens by fixed mononuclear phagocytes. Confrontation of phagocytes with particulate matter appearing in pathologic states (viruses, immune complexes, damaged erythrocytes in sickle cell anemia and other hemoglobinopathies) diverts them from their normal task of clearing opsonized encapsulated microorganisms. Corticosteroids impair the phagocytic capacity by an unknown mechanism. Major impediments to progress in this field are inadequate assays for phagocytosis and the difficulty in measuring phagocytosis in the intact organism.

139. Septic shock in a pregnant or recently pregnant woman. D. Cavanagh. Postgrad. Med. 62: 62-65, 1977.

The term "shock" refers to a condition in which the circulating blood volume is less than the capacity of the vascular bed. This disparity

results in hypotension, reduced tissue perfusion of vital organs, cellular hypoxia, and if allowed to continue, cellular death. "Septic shock" is shock associated with infection (most commonly caused by gram-negative bacilli) and is also called gram-negative or endotoxic shock. The prevalence of gram-negative sepsis among hospitalized patients has increased more than tenfold in the past 20 years. The mortality of septic shock in reported series has ranged from 11% to 82% and has averaged 50%. Obstetric patients at particular risk for septic shock include those with infected abortion, chorioamnionitis, or pyelonephritis.

The essentials of management of septic shock in a pregnant or recently pregnant woman are outlined:

- 1) Make sure that the patient has an adequate airway.
- 2) Replace fluid and blood loss. Lactate should not be used to correct acidosis because conversion to bicarbonate requires aerobic metabolism. Sodium bicarbonate acts rapidly and provides good buffering action.
- 3) Select antibiotics according to results of tests of urine and cervical secretions.
- 4) Administer glucocorticoid in pharmacologic doses.

140. Protection against endotoxin shock and impaired glucose homeostasis with ATP. J. P. Filkins and B. J. Buchanan. Circ. Shock 4: 253-258, 1977.

ATP-Mg<sup>++</sup> increased the LD<sub>50</sub> for *Salmonella enteritidis* lipopolysaccharide (endotoxin) in male Holtzman rats from 1.3 to 6.0 mg/rat. While endotoxin at 3 mg/rat iv 5 hr previously induced hypoglycemia to 12±4 mg/dl, ATP cotreatment blunted the hypoglycemia; i.e., plasma glucose values were 78±6 mg/dl. ATP treatment prevented the depression in gluconeogenesis induced by endotoxin as evaluated in vivo by the conversion of <sup>14</sup>C-alanine to <sup>14</sup>C-glucose. ATP treatment also reduced the hypercatabolism of U-<sup>14</sup>C-glucose to <sup>14</sup>CO<sub>2</sub> in vivo and by epididymal fat pads in vitro. A role for ATP in preventing disruption of glucose homeostasis and development of endotoxin shock via counteracting insulin is suggested.

141. Role of colonic bacteria in the pathophysiology of fecal peritonitis. R. D. Rink, B. L. Short, N. Van Van, and D. E. Fry. Circ. Shock 4: 259-270, 1977.

This study was designed to clarify the role of colonic bacteria in the reactions accompanying fecal peritonitis. Rats were subjected to septic or nonseptic peritonitis induced by fresh fecal suspensions or suspensions pretreated with heat or antibiotic. Measurements during 8 hr in rats with septic peritonitis recorded bacteremia, hypoglycemia and progressive hemoconcentration, lactacidemia, and hypocapnea. Mortality was 100% by 24 hr. Nonseptic peritonitis produced significantly lesser degrees of hemoconcentration and hypocapnea. Plasma lactate remained in control ranges while plasma glucose concentrations increased slightly. Mortality was 5% in 24 hr. Parameters in control rats were stable over 8 hr. Hepatic oxygen supply was estimated in each group by multiple platinum wire electrodes. Severe hepatic hypoxia was recorded by 6 hr in rats with septic peritonitis. By contrast, nonseptic peritonitis caused a comparatively mild degree of hypoxia. The pathophysiologic developments in septic rats appear to be largely the result of hypovolemia induced by colonic bacteria. Administration of a colloid solution was effective in preventing its development.

142. Effect of dopamine infusion on the hemodynamics of normal and sympathectomized rhesus monkeys in endotoxin shock. B. D. Bhagat, P. S. Rao, S. S. Gandhi, and D. Cavanagh. Circ. Shock 4: 271-278, 1977.

Infusion of endotoxin in chemically sympathectomized monkeys caused a fall in the mean aortic pressure, but the cardiac output, stroke volume, and central venous pressure were well maintained. Endotoxin-induced tachycardia in monkeys with functional sympathetics was not seen in the sympathectomized animals. Infusion of dopamine improved the hemodynamic and cardiovascular status, probably by causing vasoconstriction of the splenic and hepatic artery where the pooling of blood is believed to occur in endotoxin shock. However, these beneficial effects were not apparent when dopamine was administered in the chemically sympathectomized animal infused with endotoxin. Since chemical sympathectomy did not affect the endotoxin-induced decline in the systolic and mean aortic pressure or the severity of the endotoxin shock, it is suggested that catecholamines may not be the primary initiator or trigger substances in endotoxin shock.

143. Endocrine activation and altered muscle metabolism after hemorrhagic shock. N. T. Ryan, B. C. George, C. L. Harlow, J. M. Hiebert, and R. H. Egdahl. Am. J. Physiol. 233: E439-E444, 1977.

Studies were conducted to examine glucose and amino acid metabolism by skeletal muscle isolated from rhesus monkeys before and sequentially after an episode of resuscitated hemorrhagic shock. After shock and reinfusion, the tissue exhibited decreased effect of insulin on glucose utilization, increased leucine oxidation, and a reduced rate of leucine incorporation into protein. These changes were observed 15 min after reinfusion and persisted in part for at least 3 days. All of the observed abnormalities were more pronounced 24 hr after shock and reinfusion than 15 min after and returned to normal by 2-4 wk. The shock-induced metabolic abnormalities in skeletal muscle occurred in spite of prevention of shock-induced adrenal steroid and catecholamine secretion and of changes in blood insulin concentration using adrenalectomized-streptozotocin diabetic monkeys receiving replacement cortisol and insulin infusions. This study thus demonstrated that hemorrhagic shock in rhesus monkeys was followed by insulin resistance plus abnormalities of glucose and amino acid metabolism by skeletal muscle that were not dependent on the concurrent changes in plasma levels of adrenal steroids or catecholamines or on altered circulating insulin levels associated with shock.

144. Effect of *Shigella sonnei* endotoxin on the cholinergic control of the intestinal circulation. Y. P. Galaguza. Bull. Exp. Biol. Med. 83: 302-304, 1977.

The effect of *Shigella sonnei* endotoxin on the cholinergic control of the cardiovascular system was studied by an extracorporeal autoperfusion method with resistography of the intestinal vessels and synchronous multichannel recording of the parameters of the systemic circulation in experiments on *Macaca rhesus*. The development of toxemia was shown to be accompanied by changes in the cholinergic regulation and subsequent disturbance of the intestinal and systemic circulation. It is suggested that damage to cholinergic regulatory structures and disturbance of the circulation determine the development and course of the infectious process.

145. Prophylactic granulocyte transfusions. J. M. Ford and M. H. Cullen. Exp. Hemat. 5 (Suppl.): 65-72, 1977.

Granulocyte (PMN) transfusions were introduced in the mid-1960's and have since found increasing application in the management of infected granulocytopenic patients. A statistically significant advantage is claimed in the patients treated with antibiotics plus PMNs over controls given antibiotics alone. Animal studies have shown that when severe tissue infection is present the normal marrow releases enormous quantities of extra PMNs. It seems likely that investigators are transfusing the minimum quantity of cells required to demonstrate an effect. The number of PMNs needed to prevent sepsis may be much smaller than that required to treat established tissue infection. This possibility has generated interest in the role of prophylactic PMN transfusions. If proved successful the high cost of this approach would be offset by a reduction in morbidity and mortality, and by savings in the expensive investigation and treatment of pyrexial episodes. The benefits of therapeutic PMN transfusions have proved extremely difficult to quantitate accurately, owing to the complex clinical circumstances in which they are given. It is difficult to decide the criteria on which to judge the effectiveness of prophylactic transfusion courses. A crucial dilemma arises if patients on prophylactic transfusions develop pyrexia. Does this mean that prophylaxis has failed, or should death of the patient be taken as the only truly evaluable end-point? How are pyrexial episodes assessed in which no infective cause is ever demonstrated? With these questions in mind, two published animal studies and a clinical trial performed at St. Bartholomew's Hospital, London, in adults with acute leukaemia, are examined.

It should be noted carefully that the design of both animal studies bears little relationship to the situation as it pertains in clinical practice. Patients with leukaemia have a primary disease of the bone marrow, while patients with solid tumours may have a compromised marrow reserve. A criticism common to both experiments is the failure to use antibiotics in the controls. Antibiotics might have proved as effective at a fraction of the cost and would certainly be used in equivalent human controls. The dilemma of interpretation posed when the transfused animals develop pyrexias was avoided by both groups. Tobias et al. (Blood 47: 473, 1976) did not record temperature. In the dog model the transfused animals could be febrile before the transfusions, in which circumstances they can hardly be regarded as prophylactic.

146. Standards for filtration leucapheresis--a prerequisite for further development. I. Djerassi, J. M. Goldman, and K. H. Murray. Exp. Hemat. 5 (Suppl): 49-56, 1977.

The need to collect normal human granulocytes (PMNs) by a safe method that is simpler and more efficient than continuous flow centrifugation (CFC) is generally recognised. Filtration leucapheresis (FL) was developed and improved as a potential answer to this need. Most investigators agree that filtered PMNs are clinically effective against infections in leucopenic recipients. Points of general agreement:

- 1) One can collect large quantities of PMNs with this technique.
- 2) The procedure is easy to use.
- 3) The equipment is simple and inexpensive.
- 4) The filtered cells are effective clinically in leucopenic recipients with infection, be they animals or human.
- 5) Pyrexial reactions in the recipients are common.
- 6) The severity of the reactions is reduced by slow infusion of the cells

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- 4) The filtered cells are effective clinically in leucopenic recipients with infection, be they animals or human.
- 5) Pyrexial reactions in the recipients are common.
- 6) The severity of the reactions is reduced by slow infusion of the cells

over many hours.

7) The reactions can be minimized by premedication of the patient with steroids and/or antihistamines.

147. Platelet and granulocyte transfusion therapy. K. B. McCredie. Postgrad. Med. 62: 151-153, 1977.

Platelets and granulocytes together probably represent less than 1% of the total blood volume. In a hematocrit tube, they appear as a thin, cream-colored layer between the plasma and the erythrocytes. Consequently, in the past they have been relatively difficult to collect, concentrate, and transfuse. To give enough platelets to prevent bleeding, 4 to 20 units of whole blood would be required, and to give enough granulocytes to control infection, about 40 units of whole blood probably would be required. Obviously, transfusing such large volumes is impossible. This problem has been overcome by the development of effective methods for collection and transfusion of platelets and granulocytes.

Leukocytes are collected by continuous-flow centrifugation. The plasma and erythrocytes are recombined and returned to the donor. Recipients selected were patients with granulocytoepnia who have an infection that is unresponsive to multiple antibiotics. Granulocytopenia is defined as a granulocyte count of less than  $1 \times 10^9$ /liter. The medium granulocyte count of the patients in this study at the time of transfusion was  $0.2 \times 10^9$ /liter, so a large number of patients had no granulocytes at all. The infections usually were caused by gram-negative organisms. By the time granulocyte transfusion therapy is started, the organism is identified; the most common in this study were Klebsiella and Escherichia coli, but disseminated Candida infections also have been a major problem. In the authors' previous experience, 80% of the patients who failed to respond to antibiotics within 4 days died of infection. The average circulation time of a granulocyte in the peripheral blood is approximately 6 hours.

148. Detection of endotoxin in plasma and ascitic fluid of patients with cirrhosis: Its clinical significance. K. Tarao, K. So, T. Moroi, T. Ikeuchi, T. Suyama, O. Endo, and K. Fukushima. Gastroenterology 73: 539-542, 1977.

In the present study, endotoxin was measured by the Limulus assay in plasma and ascites in 46 patients with cirrhosis having demonstrable esophageal varices, of whom 29 had ascites and 17 did not. It was positive in ascitic fluid in 23 (79.3%) of the former group. In plasma, a positive test was obtained in 22 (75.9%) in the group with ascites and only 4 (23.5%) without ascites, the difference being significant. Of the 23 positive ascites specimens, 17 showed high titers. Hepatic uptake of  $^{198}\text{Au}$  colloid was markedly reduced in 11 of the 17 patients with endotoxemia who were studied by scanning. Death occurred within 6 months in 47.8% of the patients with a positive endotoxin test, whereas only 16.7% of those with a negative test died in the same period. No hypotension was noted in patients with toxemia and only 2 ran a fever above  $37.5^\circ\text{C}$ . Development of tolerance to endotoxin is suspected. A follow-up study has demonstrated sustained endotoxemia in some of these patients.

149. Blood coagulation in the horseshoe crab (*Limulus polyphemus*): A model for mammalian coagulation and hemostasis. J. Levin. In: Animal Models of Thrombosis and Hemorrhagic Diseases, NIH Public Health Service, DHEW Publication No. (NIH) 76-982, pg. 87-102, 1975.

The amebocyte is the only type of circulating cell in the blood of *Limulus polyphemus*, the horseshoe crab. It is a nucleated cell, the cytoplasm of which is packed with granules. When *Limulus* blood is shed or exposed to bacterial endotoxins, there is rapid aggregation of the amebocytes. Amebocytes contain all components of the coagulation system of *Limulus* blood. Extracts of washed amebocytes (amebocyte lysate) are gelled following incubation with bacterial endotoxins. Therefore, it is important to discriminate between aggregation of amebocytes and the subsequent coagulation of blood, which can occur only after disruption of amebocytes and their granules, with release of the various factors required for coagulation. It appears that the factors required for blood coagulation in *Limulus* are contained within the cytoplasmic granules of the amebocytes and are released into the surrounding medium (i.e., into the plasma, *in vivo*) following disruption of the granules.

Data indicate that the coagulation system of *Limulus* is contained exclusively within the amebocytes, which circulate in the blood. Recent studies suggest that factors necessary for blood coagulation are localized within the cytoplasmic granules of amebocytes. Aggregation and disruption of cells follow exposure of amebocytes to foreign surfaces. Endotoxin produces similar changes and, in addition, results in coagulation of the blood. Heparin or calcium and magnesium-free solutions do not prevent coagulation. In the absence of endotoxin, disruption of amebocytes, *in vitro*, is not followed by the coagulation of blood, despite the release into the plasma of the factors required for coagulation.

Phagocytosis has not been reported in amebocytes, although definitive studies have not yet been done. In contrast, although this is not considered one of their primary functions, platelets are capable of phagocytosis and have been shown to have limited bactericidal activity. Amebocytes, which clearly play an important role in the control of bacterial infection by sealing wounds and trapping bacteria in masses of gel also have been shown to have some bactericidal activity.

Endotoxin, a lipopolysaccharide present in the cell wall of all gram-negative organisms, is capable of interacting with amebocytes or platelets and of triggering blood coagulation. Blood coagulation in rabbits is activated by endotoxin; in fact, this is the only animal in which the Shwartzman reaction can be produced by two sequential injections of endotoxin. In contrast, the platelets of humans and other primates are relatively resistant to the effects of endotoxin. The rudimentary ability of mammalian platelets to phagocytose particles and kill bacteria may be another remnant of functions that are more important in amebocytes (or thrombocytes of other invertebrates).

150. The effect of glucagon and blood transfusion on hepatic circulation and oxygen consumption in hemorrhagic shock. B. Lindberg and N. Darle. J. Surg. Res. 23: 257-263, 1977.

Both experimental and clinical data indicate that anoxic damage to the liver plays a major part when patients succumb after a period of shock. In a previous study it was found that treatment by blood transfusion after 30 min of hemorrhagic shock in the pig restored the initial liver blood flow and increased

the oxygen consumption. The aim of this study was to investigate whether injection of glucagon combined with blood transfusions could further increase liver blood flow and oxygen consumption in the treatment of hemorrhagic shock.

Ten pigs were subjected to a standard shock model, including two 30-min periods of hemorrhagic shock at 50 mmHg. After the first period of shock, treatment was given with glucagon and transfusion of the shed blood. Portal vein and hepatic artery flow as well as oxygen consumption were measured. Both periods of shock resulted in a marked decrease in blood flow as well as oxygen consumption. Treatment with glucagon and blood transfusion resulted in an increase in hepatic artery flow to 300% of the preshock value but no significant increase in the portal vein flow compared with blood transfusion alone. The high hepatic artery flow caused a very high inflow of oxygen to the liver. In spite of this high inflow of oxygen, the oxygen consumption of the liver was not significantly higher than after blood transfusion alone.

151. Interaction between syntoxic and catatoxic steroids on endotoxin lethality in relation to liver metabolism in mice. G. Lazar, S. Sekiya, and M. K. Agarwal. J. Reticuloendo. Soc. 22: 13-20, 1977.

Bacterial endotoxins evoke a wide variety of responses in the host. Despite a voluminous literature, the factor(s) responsible for toxicity, tolerance and pharmacologic protection against lethality remain unknown. Syntoxic steroids, such as cortisone, protect against endotoxin lethality probably by changes in the induction of liver enzymes, gluconeogenesis and modulation of the activity of the reticuloendothelial system (RES). Selected catatoxic steroids, such as pregnenolone-16 $\alpha$ -carbonitrile (PCN), are known to induce hepatic microsomal enzymes and to oppose a wide variety of processes responsive to modulation by syntoxic steroids. It was of interest, therefore, to investigate the influence of PCN on endotoxin lethality and its reversal by cortisone.

The ability of the catatoxic steroid pregnenolone-16 $\alpha$ -carbonitrile (PCN) was studied in relation to its ability to alter cortisone protection against endotoxic death. The 3-day pretreatment with PCN (total of 18 mg) sensitized mice to endotoxin lethality and this was associated with normal carbon clearance rates and considerable hepatomegaly. Cortisone protected these animals against endotoxin lethality, induced liver tryptophan pyrrolase and tyrosine transaminase activities, but gluconeogenesis remained impaired in mice treated with PCN.

152. Effects of acute endotoxemia on glucoregulation in normal and diabetic subjects. E. J. Rayfield, R. T. Curnow, D. Reinhard, and N. M. Kochicheril. J. Clin. Endocrin. Metab. 45: 513-521, 1977.

Response to the endotoxin, *Pseudomonas* polysaccharide (Piromen), was used as a model for infection induced insulin resistance in seven control subjects and seven juvenile diabetics. Following endotoxin the control subjects developed fasting hyperglycemia, mild glucose intolerance, basal and glucose stimulated hyperinsulinemia, hyperglucagonemia, and elevated plasma levels of growth hormone, ACTH, and cortisol. In the diabetic subjects given endotoxin, basal glucose values and those following iv GTT-2 were unchanged from comparable values during GTT-1, although plasma glucagon, growth hormone, cortisol and ACTH all became significantly elevated. The diabetics required 31% more insulin on the endotoxin day than the control day, despite the fact that glucose values were 83% higher on the endotoxin day.

The current data suggest that constant low-dose insulin infusion blunted endotoxin induced growth hormone release and prevented further deterioration in glucose intolerance in juvenile onset diabetics. In contrast, cortisol responses were greater in diabetic subjects following endotoxin than in normal controls despite the infusion of low-dose insulin. The insulin resistance which developed in the diabetic subjects following endotoxin in the present study as documented by increase in insulin requirements with significantly higher mean plasma glucose levels is in accord with the well known difficulty achieving good glucose control in an infected diabetic patient.

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